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# Editorial

## The Physician's Continuing Education

*Summary of a Report of the Status and Objectives of Postgraduate Medical Education by the Committee on Professional Education of the American Heart Association.**

AN ANALYSIS of postgraduate education in this country raises doubts as to how far programs, as they are presently planned and conducted, succeed in raising the level of medical practice. If the ultimate goal of professional education is the improvement of patient care, then the physician must be provided with better opportunities to keep abreast of medical advances and to cultivate his skills and judgment.

The fact that programs frequently are not adapted to their needs may be a reason why many physicians are not taking advantage of the opportunities they now have. D. D. Vollan in his survey[1] for the American Medical Association found that too few physicians keep in touch with advances in medicine through continued education. This is true of recent graduates, as well as of physicians long in practice, since an estimated one third of current graduates do not undertake any sort of continuing education. The American Academy of Medicine succeeds in attracting only about 20 per cent of general practitioners to its lectures and courses. To strengthen the physician's motivation for learning, his characteristics, attitudes, and needs must be better understood.

### Planning a Realistic Program

Although the quality and technics of postgraduate education have not been adequately assessed, it is clear that lack of physician interest often can be attributed to the type of program offered. When programs are designed without identifying the specific audience for which they are intended and when the learner-physician is not included at the planning stage, both learner and teacher are placed at a disadvantage. The teacher is not prepared for the kind of audience he is to address, and the learner becomes the passive recipient of knowledge that may not be geared to his needs.

*This report was prepared at the request of the American Heart Association's Central Committee on Medical and Community Program for a five-year projection of activities for the Association in professional education.

To define the fundamental problems of physician education, the Committee on Professional Education met with representatives of the Professional Education Committees of the affiliate heart associations during the 1959 Annual Meeting of the American Heart Association, and subsequently with a group of consultants and medical educators at a two-day study session in January 1960.

From these sessions it became apparent that to recommend a program of activities for the American Heart Association would require a general analysis of the status of professional education in this country and of current teaching methods.

Copies of the *complete* report may be obtained from local Heart Associations or through the American Heart Association, 44 East 23rd Street, New York 10, New York.

Physicians who ask for "something practical" in program planning are not satisfied with didactic and textbookish presentations. Those with a keen interest in continuing education are repelled, while others who need to be inspired are not attracted. Objections to "too high a level" usually refer to technical esoterica rather than to solid scientific content.

Lectures, panel discussions, seminars, motion pictures, and exhibits too often impart information only in a passive manner. Opportunities for bedside teaching, conferences, and courses in which the physician actively participates have been few.

In attempts to keep the physician up to date with medical advances, there has been too much reliance on the distribution of medical literature. The practicing physician has little time for reading and is unprepared to sift the mass of material that inundates him from many sources. The pharmaceutical houses have recognized the physician's dilemma by providing him with information in palatable, readily assimilated form. This kind of material, however, does not encourage self-education if the physician accepts it as providing easy "answers" without exercising his critical judgment. Medical literature is a key instrument in the continuing education of the physician, but it cannot perform the whole function.

### Studying the Physician Himself

Before realistic programs of education can be planned, a great deal more information about the practitioner himself must be secured. The physician is the product of many influences—his experience in medical school, the standards of medical practice in his community, the competition he must meet, the patient load he carries, and his own ambitions and personal problems. It is imperative to study the practitioner from many aspects.

The study by D. D. Vollan,[1] two studies by the American Heart Association,[2, 3] and a survey by the American Cancer Society have thrown some light on the characteristics of the practicing physician and on the effectiveness of professional education. A recent survey of North Carolina general practice by Peterson and associates[4] investigated the needs of practicing physicians and the reasons why many do not take advantage of opportunities for continuing education.

In direct observation of medical practice, Peterson and his associates came to the tentative conclusion that the deficiencies of medical training may account for the poor performance of those physicians who appear to lack a comprehensive grasp of clinical skills. The report suggests that medical-school training might be more effective if it were geared to the individual's competence and capabilities for learning. Since individuals do not learn at the same rate, it is unreasonable to expect that all physicians will receive equal benefit from the same educational program.

The Peterson report also points out other important areas for further investigation: identification of the attributes and characteristics of the individual who will make a successful student and practitioner of medicine, and studies of the favorable influence of practice in association with a partner or a group.

### Appraising the Methods

Peterson was unable to document the influence of postgraduate study on the physician's performance, but his data suggest that a reappraisal of the methods now employed in postgraduate education is urgently needed. Vollan, in his report, emphasized that physician education requires long-term planning by the sponsoring groups, including an analysis of the over-all needs of the physicians in given areas and the development of an integrated program.

The elaborate structure of contemporary postgraduate medical education has been built with little regard for the science of learning. The learner for the most part has been the recipient of wisdom dispensed by those who assume they know what he needs. The focus should shift from concentration on courses, recruitment of speakers, and development of materials to determining first what the phy-

sician-learner himself identifies as his educational needs. In this way his horizon may be broadened to recognize that he needs more knowledge than he presently desires. Teachers should be as carefully selected for their skill in teaching, as for their reputation as scientists or specialists.

Medicine as an art has been defined by Dana W. Atchley[5] as the cultivation of attitudes among physicians that lead to their increasing ability to evaluate evidence and to analyze clinical problems. The plan and content of postgraduate education should have this objective in view. Teaching devices, whether they be in the form of lectures, symposia, panels, or group discussions, should allow for maximum participation by the learner if he is to improve his skill in interpreting clinical data.

Intensive bedside teaching, valuable to any physician, is essential to those in need of refresher education. This is available to physicians near medical schools and clinical centers, but the community hospital has been neglected as a setting for learner participation. The private community hospital should be developed as a prime unit of continuing education for the physician, with ward rounds, conferences, clinics, and periodic staff meetings devoted to learning.

The consecutive case conference has been a successful means of teaching moderately large groups with considerable participation by the learner. A critical review of how the physician handles a case has such educational value for him that it should overrule personal pride or other considerations.

In recent years, the Annual Scientific Sessions of the American Heart Association have provided a program of clinical sessions reviewing important cardiovascular areas. These sessions might be offered on a more limited membership basis to allow for greater learner participation.

### Reaching the Practitioner and the Specialist

The costs of postgraduate medical education and limitations in budget and personnel often necessitate cooperative effort on the part of several educational organizations. This is an advantage, because duplication can be avoided, programs can be more comprehensive, and a larger audience can be reached. Sometimes organizations are overanxious about loss of identity in cooperative planning. In the case of heart associations, it is not suggested that they delegate all responsibilities to other agencies, but that they bring together multiple resources to solve common problems. In so doing, they will best serve the interests of postgraduate medical education.

In joint action of this kind, the participating agencies should review together the total needs of professional education in the community and plan a variety of programs to capture the interest of both the general practitioner and the specialist.

The family physician should be motivated toward continuing education so that he can meet the demands of modern medicine which require diagnostic skill and judgment. Even though his competence cannot lie in every technical sphere, he should not relinquish his responsibility to analyze clinical problems.

Although the internist and pediatrician may be better informed of new advances in medicine, this group needs to develop a more comprehensive view of the patient as a person and of illness as an aspect of the patient's adaptation to his problems. The cardiologist and cardiovascular surgeon, because they often assume the responsibility of diagnosis and treatment, also need to understand the patient's emotional development and his social adaptation to diminished cardiovascular function.

The American Heart Association has a particular responsibility to specialists in the cardiovascular field. Its program must meet the level of technical sophistication of the cardiologist and cardiovascular surgeon and at the same time encourage this group to adopt the concept of comprehensive care.

### Evaluating Medical Education

A study of the impact of educational programs on the skill and judgment of physicians is urgently needed. It is essential to assess

what degree of intellectual growth has been achieved and to identify the responsible factors. There is a wide spectrum of potential research activities in professional education, ranging from evaluation of present methods of teaching to the development of new educational approaches.

Research in medical education faces methodologic problems inherent in all social and behavioral research: it must take into account the many factors contributing to the development of the ideal physician. These problems can be solved only by teamwork between medical teachers who know the field of medicine and general educators who are familiar with educational concepts and methods.

The experiment in Colorado by Hammond and Kern,[6] although concerned with medical students, resulted in several important conclusions that, with some modifications, may be applicable to analysis of postgraduate education. The study shows that considerable time must be given to planning a subject, and it emphasizes the need for thorough orientation of both teachers and learners before a pilot program is started. More importantly, this report demonstrates that, under controllable conditions, methods can be developed to measure many of the contributing factors and some of the effects of a broad, educational effort.

Although research activities in professional education are more particularly in the province of the medical school and the departments of postgraduate medical education, they should be of interest to any organization dealing with professional education, such as the American Heart Association.

**The Role of the American Heart Association**

Both in research and in other aspects of professional education, the American Heart Association must take the broad view that the imparting of knowledge and skills to physicians goes beyond the cardiovascular field alone. The programs of other agencies, with whom collaboration is essential, must be considered, too.

The Committee on Professional Education suggests that the American Heart Association form a commission with other voluntary agencies to establish a cooperative plan for professional education, with participation of the American College of Physicians, American College of Surgeons, American Academy of General Practice, Association of American Medical Colleges, the American Medical Association, and the Association of Hospital Directors of Medical Education. A full-time coordinator may be needed to plan with these groups and to insure the cooperation of community hospitals and postgraduate education departments of medical schools. Joint study programs should be explored with medical schools that have established divisions of research in medical education, such as the University of Illinois, Western Reserve University, and the Medical College of Virginia.

In the opinion of the Committee, the most productive approach to physician education is through the development and evaluation of pilot programs. It was recommended that the American Heart Association develop pilot projects in places where the assistance of affiliate heart associations can be most effective, and that procedures be set up to encourage the collaboration of other agencies and institutions interested in continuing physician education. A design for evaluating its effectiveness should be included in the plan of each project.

To support these programs, considerably larger funds will be required than those now being spent for conventional methods with the results not always certain. The Committee urged the American Heart Association's Board of Directors to approve the sum of $50,000 as an assurance that a well-organized and vigorous program can be planned for the year 1961-1962, with research in medical education the basic purpose. Pilot programs suggested in the Committee's recommendations were:

Studies of medical practice in representative localities

Teaching programs in community hospitals

Teaching programs in rural areas

Self-teaching methods for the physician (a correspondence course and other educational materials)

Consecutive case conferences

Conferences for medical teachers to demonstrate modern teaching methods.

It was also recommended that the American Heart Association employ the services of a person qualified to work with the national staff on the preparation, supervision, and evaluation of each pilot study. Whatever form coordinated efforts on the affiliate and national levels of the Association may assume, the need for competent design and evaluation of each program will be of paramount importance.

### The Future of Professional Education

It is evident that if postgraduate medical education is to achieve its objectives, it must provide for more intensive learner participation and more skillful teaching. The conventional methods now used in the continuing education of a physician, such as lectures and printed materials, are no longer adequate to convey the expanding knowledge and complicated skills of modern medicine.

The physician of tomorrow must be well informed because he will have at his disposal more effective and potentially harmful drugs than ever before. Furthermore, with ease of communication and the technological requirements for diagnosis and treatment, the range of responsibility has increased for all physicians including the rural practitioner.

At the expense of a proper concern for quality, there is a disproportionate emphasis on the number of physicians available in the country and on the ratio of physicians to patients in a community. It seems likely in the future that problems of maintaining quality and comprehensiveness of medical care will outweigh those of number and distribution of physicians. Medical schools are graduating more physicians than 25 years ago, but the quality of the applicants is generally considered poorer.[7] The problems start with undergraduate education and become more acute at the postgraduate level.

It is becoming more and more evident that all practicing physicians need continuing medical education. If institutions and organizations presently engaged in professional education cannot meet the needs, the time may come when an official agency will have to assume the responsibility. For this reason, voluntary agencies should not delay in taking a new and more vigorous approach to their problems. They must cooperate in supplying the leadership and staff for a long-range program that will be acceptable to the profession and effective in providing comprehensive and continuing postgraduate education.

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(1959-1961)

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## The Early History of Instrumental Precision in Medicine

When Galileo, but eighteen years of age, a student of medicine, counted the vibrations of the great bronze lamp swinging in the gloom of the Duomo of Pisa, he conceived them to be in equal time. Desiring to test the truth of his conclusion, he is said to have used his own pulse as a measure of the correctness of the pendulum. Forty years later, in describing the accuracy of his first clock-work, he says with enthusiasm, "My clock will not vary so much as the beat of a pulse." Says Viviani, his biographer, "The unerring regularity of the swing of a suspended lamp suggested to the young medical student the reversed idea of marking with his pendulum the rate and variation of the pulse. Such an instrument he constructed after a long series of experiments. Though imperfect, it was hailed with wonder and delight by the physicians of the day, and was soon taken into general use." Unclaimed by Galileo, it was attributed to Paolo Sarpi, and clearly enough was appropriated at a later date by that notable genius, Sanctorius, who also, like Galileo, called it the pulsilogon. . . . It is interesting to observe the tendency towards securing accuracy in medicine thus shown by Galileo at the outset of his medical career. . . . With his thermometer and the pulsilogon, and with this picture of his testing the accuracy of the swing of the lamp by his own pulse, this marvelous mind passes out of medical history. Where he would have left it had he remained with us, who indeed can say? Of his loss to us, a poet has spoken:

Ah! when in Pisa's dome
He watched the lamp swing constant in its arc,
He gave to man another punctual slave,
And bade it time for us the throbbing pulse.
Not that grave Harvey whom Fabricius taught,
Not sad Servetus, nor that daring soul,
Our brave Vesalius, e'er had matched his power
To read the riddles of this mortal frame.
And then he left us. Would our strange machine
Had kept his toil, and cheated heaven's fair stars!

—S. WEIR MITCHELL, M.D., *Transactions of the Congress of American Physicians and Surgeons,* Second Triennial Session held at Washington, D.C., 1891. New Haven, The Congress, 1892, p. 173.

# Gangrene of Lower Extremity Secondary to Extensive Venous Occlusion

*By* JAMES V. ROSS, JR., M.D., ARCHIE H. BAGGENSTOSS, M.D., AND JOHN L. JUERGENS, M.D.

GANGRENE of an extremity caused by venous occlusion without associated arterial occlusion is uncommon. Haimovici[1] noted that Fabricus Hildanus, in 1593, apparently recognized the possibility of gangrene of venous origin; it was not until 1859, however, that Heuter[2] reported a case, giving an excellent account of the clinical and pathologic criteria of this type of gangrene. Grégoire,[3] in 1938, coined the term "phlegmasia cerulea dolens" to denote extensive venous occlusion that is characterized by cyanosis, ischemia, woody edema, violaceous discoloration, ecchymosis, and transient loss or reduction of arterial pulsations. Like Trémolières and Véran,[4] who described this condition in 1929, Grégoire attributed the ischemia to secondary arteriospasm.

Buerger,[5] in a book published in 1924, mentioned only that complete obstruction of the chief veins of a part without occlusion of the arteries, may also lead to gangrene, although this is of rare occurrence. It was not until 1938 that Tilley[6] made the first report of this condition in the American literature; in the same year, Pringle[7] documented the first two cases in the English literature. In Tilley's three cases, clinical data are lacking, but careful dissection of the amputated limbs revealed "obstruction of all the veins; the arteries were grossly normal and no obstruction could be demonstrated."

Ten years later, Haimovici and Suffness[8] reported a fourth case in the American literature and again brought the clinicopathologic characteristics to the attention of physicians in the United States. Although sporadic reports of phlegmasia cerulea dolens have appeared subsequently in the American literature,[9-18] we have been able to collect records of only 13 cases with gangrene since Tilley's[6] three cases in 1938.[8-18] Although the possibility of gangrene owing to venous occlusion alone has been commented on by Homans,[19] Samuels,[20] and Allen and associates,[21] other specific case reports have not appeared. This attests to the fact that gangrene caused by venous occlusion without associated arterial occlusion is indeed uncommon or is unrecognized by American physicians.

### Methods and Materials

A study was made of the records of patients at the Mayo Clinic who had gangrene apparently produced by venous occlusion during the 31-year period from 1929 through 1959. A total of 16 patients appeared on a clinical basis to have this unusual type of gangrene. Two cases were discarded, however, because of associated diabetes mellitus and infection, one case was discarded because of a past history of embolic phenomena, and two cases were discarded because of arterial thrombosis; these associated findings cast some doubt on the cause of the gangrene. Among the 11 remaining cases, pathologic material was available for study in nine, and the two remaining cases were thought to have been subjected to adequate clinical investigation to warrant inclusion.

The clinical criteria for inclusion in the present study were (1) the clinical appearance of extensive venous thrombosis, (2) the evolution of gangrene in an edematous, cyanotic limb, and (3) palpable arterial pulsations in the affected extremity at the time of the appearance of gangrene.

The pathologic criteria were (1) thrombosis of the major venous channels of the affected limb, (2) patency of the major arteries of the same limb, and (3) gangrene of the limb. In three specimens, extensive pathologic examination of the major veins and arteries of the involved extremity was done. In an additional specimen, fluid was injected from the common iliac artery to the dorsalis pedis artery as further evidence of a patent arterial system.

From the Mayo Clinic and the Mayo Foundation, Rochester, Minnesota.

**Figure 1**

*Case 5. Extensive thrombosis above and below Nylon graft.*

The records were reviewed with particular regard to (1) underlying disease, (2) treatment with anticoagulant drugs and sympathetic-blocking agents, (3) the development of acute peripheral circulatory failure, and (4) the cause of death.

## Results

The 11 patients satisfying the clinical and pathologic criteria for gangrene caused by venous occlusion without associated arterial occlusion included seven females and four males ranging in age from 7 months to 75 years. The one infant was a boy. Exclusive of this infant, the average age for males was 47.3 years, for females 57.5 years, and for both males and females 52.4 years.

### Pathologic Aspects

A total of 13 gangrenous limbs were present; eight right lower extremities (in two males and six females) and five left lower extremities (in three males and two females) were affected. One male and one female had bilateral involvement.

The extent of the gangrene varied from splotchy superficial zones on the legs or on four or more toes to involvement of the lower extremity from the knee downward (table 1).

The underlying condition was neoplastic disease in six cases, chronic cardiac disease in two, thrombocytopenic purpura (with splenectomy) in one, congenital membranous valve of the urethra in one, and chronic cholecystitis and cholelithiasis in one (table 1).

The upper limit of the thrombus as shown by necropsy or postamputation pathologic examination was the iliofemoral vein in eight cases, with minimal extension into the inferior vena cava in three of these cases and moderately high extension in two; in the other three of these eight cases, the upper extent of the thrombus was in the femoral-popliteal venous system. One of the two instances of moderately high extension into the inferior vena cava occurred in a patient (case 5) who had an end-to-end Nylon prosthetic graft inserted after sacrifice of part of the inferior vena cava during excision of a rhabdomyosarcoma that did not involve the lumen of the vessel. The graft was not involved by the thrombus, which extended above and below the prosthesis at the level of the suture lines (fig. 1), with extension into the left iliofemoral vein. The other patient who had moderately high extension into the inferior vena cava was the only one to show involvement of the renal vein and histologic evidence of venous infarction of the kidney.

Of the three patients who had occlusion of the femoral-popliteal vein, two underwent surgical amputation of the affected limb. Both patients survived the operation only to die subsequently from pulmonary embolism. The

**Table 1**

*Data in 11 Cases of Gangrene of Lower Extremity due to Venous Occlusion*

| Case | Age (yr.) and sex | Underlying disease process | Upper extent of thrombosis | Extent of gangrene | Cause of death | Palpable pulses with onset of gangrene | Extent of dissection or examination |
|---|---|---|---|---|---|---|---|
| 1 | 49 F | Thrombocytopenic purpura (with splenectomy) | Bilateral iliofemoral and low inferior vena cava | Left foot and ankle, right midfoot and ankle | Peripheral vascular circulatory failure and shock | Femoral, popliteal, posterior tibial, and dorsalis pedis | To dorsalis pedis; arteries injected |
| 2 | 65 F | Adenocarcinoma of pancreas | Bilateral iliofemoral and low inferior vena cava | Right distal third of foot | Uremia | Femoral, popliteal, and posterior tibial | Popliteal and below for several inches |
| 3 | 7/12 M | Congenital membranous valve of urethra | Bilateral femoral and popliteal | Left to knee | Uremia | Femoral and popliteal; edema | Popliteal and below |
| 4 | 55 F | Old and healed subacute bacterial endocarditis and rheumatic heart disease | Left femoral and popliteal | Left distal third of foot | Pulmonary embolism | Femoral, popliteal, posterior tibial, and dorsalis pedis | Surgical specimen: midfemoral to posterior tibial and dorsalis pedis |
| 5 | 60 M | Retroperitoneal rhabdomyosarcoma | Bilateral iliofemoral and high inferior vena cava | Superficial blebs of left calf and foot | Peripheral vascular circulatory failure and shock | Femoral, popliteal, and posterior tibial | Midfemoral |
| 6 | 46 M | Squamous-cell carcinoma of bronchus | Bilateral iliofemoral | Left distal half of foot, right to midcalf | Carcinomatosis | Femoral, popliteal, posterior tibial, and dorsalis pedis | Midfemoral |
| 7 | 62 F | Adenocarcinoma of bile duct | Bilateral iliofemoral and low inferior vena cava | Right to below knee | Pulmonary embolism | Femoral, popliteal, posterior tibial, and dorsalis pedis | Midfemoral |
| 8 | 75 F | Abdominal carcinomatosis, unknown cause | —— | Right entire foot | Pulmonary embolism | Femoral, popliteal, and posterior tibial | —— |
| 9 | 43 F | Adenocarcinoma of pancreas | —— | Right first four toes | — | Femoral, popliteal, posterior tibial, and dorsalis pedis | —— |
| 10 | 55 F | Arteriosclerotic hypertensive cardiovascular disease | Junction of popliteal and femoral | Right lower two thirds calf and entire foot | Pulmonary embolism | Transient loss of popliteal and posterior tibial | Surgical specimen: femoral, popliteal, and posterior tibial |
| 11 | 36 M | Chronic cholecystitis and cholelithiasis | Bilateral iliofemoral and high inferior vena cava | Right distal two thirds foot | Uremia | Femoral, popliteal, posterior tibial, and dorsalis pedis | Lower femoral |

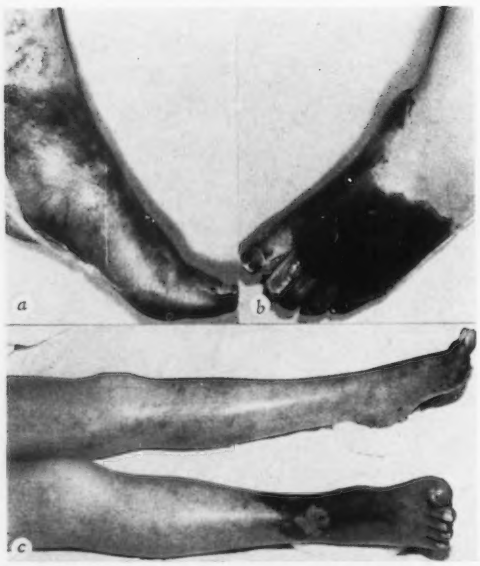


**Figure 2**

a *and* b *(Case 1). Gangrene of left midfoot and medial aspect of ankle.* c *(Case 6). Gangrene involving both feet and right ankle.*

cause of death in the 10 patients known to have died is shown in table 2. Only one patient, who had adenocarcinoma of the pancreas and gangrene of four toes, was reported to be living at the time of this study.

### Clinical Aspects

Seven of the 11 patients received anticoagulant therapy. Six of them were given anticoagulants prior to the onset of gangrene, including one patient referred to the clinic with gangrene who had been started on anticoagulant therapy at home 7 days prior to admission. The drugs used were bishydroxycoumarin (Dicumarol) in five patients, Warfarin (coumadin) sodium in two patients, and heparin by continuous intravenous drip in one patient who had received Dicumarol up to the time of the appearance of gangrene. Table 3 shows the prothrombin times in these six patients on the day prior to, the day of, or the day after the appearance of the gangrene. All prothrombin times were determined by the modified Quick one-stage method used at the clinic,[22] in which the therapeutic range is considered to be between 27 and 60 seconds; in terms of prothrombin activity, this corresponds to 30 and 10 per cent, respectively. Four patients had prothrombin times of 30 seconds or more during this period. One patient may be presumed to have been in the therapeutic range of hypoprothrombinemia, with a prothrombin time of 69 seconds on the day of admission. The sixth patient, who had a prothrombin time of 27 seconds, was still in the therapeutic range at the lowest level acceptable.

One patient underwent a right lumbar sympathetic block with the use of piperocaine (Metycaine) hydrochloride but apparently was not helped and may have been harmed by the procedure; it was the clinical impression that the block may have contributed to the more rapid appearance of massive edema, extensive cyanosis, and shock.

There appeared to be nothing distinctive in the clinical picture early in the course of the disease to forewarn the physician that the venous occlusion might lead to gangrene. The fact that all six patients who had underlying neoplastic disease also had histories of previous episodes of thrombophlebitis may be significant. A similar history should alert the physician to the possibility of gangrene due to venous occlusion.

Three patients clinically presented the picture of peripheral circulatory failure and shock, which did not respond to the intravenous administration of fluids. In one of these patients, acute pulmonary embolism was the immediate cause of death.

## Discussion

It is the absence of any significant occluding lesion within the major arteries of the affected limb that distinguishes the condition presently under consideration from the usual forms of gangrene and makes gangrene of venous origin a distinct clinicopathologic entity. Necropsy and postamputation pathologic findings of patent major arteries with extensive thrombosis of the veins in a gangrenous limb indicate the existence of this mechanism. Gangrene can be produced in dogs if the

**Table 2**

*Cause of Death in Gangrene of Lower Extremity Caused by Venous Occlusion*

| Cause of death | Cases |
|---|---|
| Pulmonary embolism | 4 |
| Uremia | 3 |
| Carcinomatosis | 1 |
| Peripheral vascular circulatory failure and shock | 2 |
| Total | 10 |

occlusion of the venous system is complete. Veal and co-workers[10] ligated the femoral vein in dogs and noted only transient edema and no gangrene. Fontaine and Pereira,[23] in their extensive study of the formation and retention of edema in limbs in which the venous return was obstructed by ligation, resection or sclerosis of the veins and lymphatics, produced gangrene in this manner. They made a complete circular incision in the upper part of the thigh in dogs, incising skin, aponeurosis, and muscle, ligating and dividing all veins but sparing all major arteries, nerves, and bones. On the evening of the day of operation, massive edema of the lower limb appeared, followed by the onset of wet gangrene 2 days later. Arteriograms of the gangrenous limb showed a normal arterial system. Arteriograms also have proved the patency of the arterial system down to the size of digital arteries in patients with this type of gangrene.[1]

The fact that the gangrene seen in this condition can be superficial and similar to that seen in frostbite or ergot poisoning raises the question of the status of the extremely small arteries and arterioles in the subcutaneous tissue. Neither in this study nor in the literature is there evidence to show that this portion of the arterial system is not occluded. Although such evidence is lacking, occlusion of these small arteries alone would not appear to be sufficient to explain the more extensive gangrene seen in some cases. Further study regarding this portion of the arterial system in this type of case is needed.

Arteriospasm, which apparently occurs in some cases,[1, 3, 4] is not a constant clinical finding and probably cannot in itself be considered the basic cause. Thus, it would appear that arterial blood can reach the tissues but is prevented from returning by extensive venous obstruction primarily and perhaps the venospasm secondarily,[24] causing stasis, hypoxia, and subsequent gangrene.[1] Gangrene could develop in any case of venous obstruction that becomes so extensive as to prevent the return of arterial blood from the affected limb. Its prevalence in the lower extremity may be related in part to the more frequent occurrence of thrombophlebitis in the lower extremity.

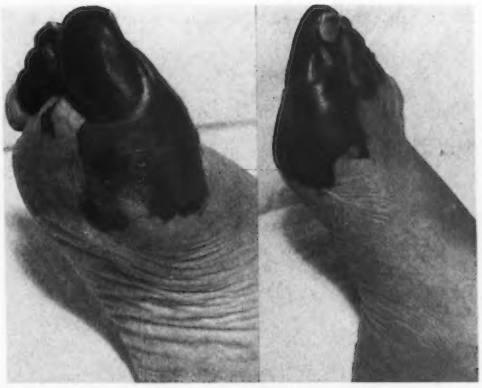

**Figure 3**

*Case 9. Gangrene of first four toes on right foot.*

Although the onset of this syndrome has been reported to occur suddenly and to mimic an arterial embolus (pseudoembolic type),[1] it was primarily a complication of extensive thrombophlebitis in this study. From an analysis of our cases, underlying neoplastic disease with its tendency for recurrent episodes of thrombophlebitis is more prone to be accompanied by this dire complication.

The use of anticoagulant therapy early and continuously throughout the course of the disease does not necessarily prevent further extension of the thrombus or the development of gangrene. On the other hand, it is impossible to assess the number of patients who have received anticoagulant treatment and in whom such therapy has prevented the development of gangrene. The basic defect is presumably a thrombosing tendency or a state of

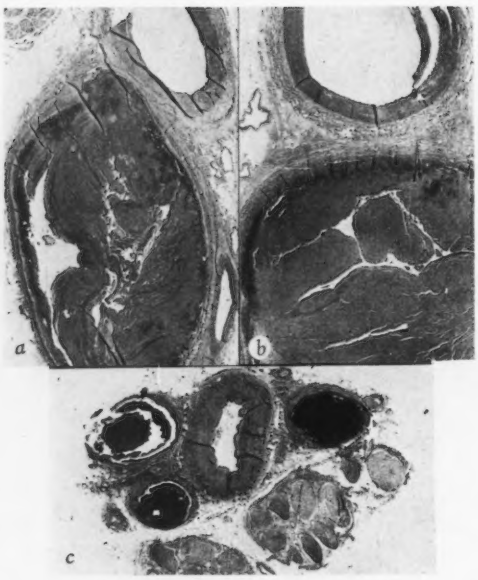


**Figure 4**

*Case 1. Extensive organizing venous thrombi, with patent arteries.* a. *Left iliac vein (hematoxylin and eosin).* b. *Left femoral vein (hematoxylin and eosin).* c. *Left posterior tibial vein and tributaries (hematoxylin and eosin).*

hypercoagulability, the mechanism of which is not completely understood despite the various theories advanced.[17, 25–27] Further study and information regarding this aspect of the disease are imperative before prophylaxis or treatment can be considered adequate. Therefore, it is logical to give anticoagulants to these patients until specific information to the contrary is forthcoming. The condition has an extremely high rate of mortality either from pulmonary embolism or the serious underlying disease, such as neoplasms.

Either or both limbs may be involved by the gangrene, but unilateral involvement is the usual occurrence, and the gangrene is restricted more often to the region below the knee, more specifically, to the ankle and foot (figs. 2 and 3). It is a wet gangrene, frequently superficial, and it appears to develop more slowly in most cases as compared to that from arterial occlusion.

Although extensive thrombosis is present

**Table 3**

*Prothrombin Times in Relationship to Onset of Gangrene of Lower Extremity Due to Venous Occlusion*

| Case | Drugs used | Prothrombin time, seconds | | |
|---|---|---|---|---|
| | | Day before gangrene | Day of gangrene | Day after gangrene |
| 1 | Dicumarol<br>Heparin | 47 | 37 | 40 |
| 2 | Dicumarol | 46 | 27 | Died |
| 6 | Dicumarol | 41 | 53 | 34 |
| 7 | Dicumarol | — | — | 69 |
| 8 | Coumadin | 37 | — | 34 |
| 9 | Coumadin | — | 31 | 46 |

in the major venous system in the affected leg (fig. 4), often with extension into the inferior vena cava, thrombosis of the renal vein and renal infarction appear to be uncommon despite clinical evidence of some renal dysfunction or insufficiency in about a third of our cases.

Peripheral circulatory failure and shock should be anticipated in the event of unrelenting and progressive massive edema. The onset of shock is an important sign of a poor prognosis. This coincides with the earlier experimental work of Perlow and associates[28] and Katz and co-workers,[29] which indicated that venous obstruction to the hind limb in a dog leads to intractable shock and death; these workers also showed that, if blood for transfusion is not available, the early use of saline, before capillary permeability is affected, combats shock and prolongs life. Administration of a solution of dextrose does not appear to prevent shock in the experimental animal.[29] However, peripheral circulatory failure and shock do not always occur in this condition.

The management of phlegmasia cerulea dolens has not been satisfactory, as shown by the numerous regimens advanced and the controversy concerning all of them. Veal and associates[10] advocated high elevation of the affected limb with regular passive flexion to express the entrapped blood, diminish venous engorgement, and allow fresh arterial blood to enter. This appears to be a reasonable approach, but the possibility of dislodging a portion of the thrombus and initiating pulmo-

nary embolism must be considered seriously.[30] The fact that five of the patients studied by Veal's group had previous femoral ligations may have protected them from emboli. Thrombectomy, originally performed by DeBakey and Ochsner[9] and more recently advocated by Mahorner,[31] should be considered, although the results have not been uniformly good. Mahorner's procedure consists of removing the thrombus and closing the vein without ligating it. Heparin may be given as a continuous infusion into a superficial vein distal to the level of the thrombectomy, usually the saphenous vein at the level of the medial malleolus, and this vein is ligated distally. Edwards[30] advocated use of lumbar sympathetic block. He reported a more rapid decrease in the elevated venous pressure after thrombectomy, but the total decline was not significantly greater than that with sympathetic block alone. Veal and associates[10] stated that measures that increase arterial flow to the affected limb should be avoided despite the questionable role of arteriospasm in this disease. The mechanism involved in the production of this type of gangrene and the occasional complication of peripheral circulatory failure and shock would appear to contraindicate such procedures. The results in our one patient who had a right lumbar sympathetic block illustrate the unfavorable effect that might result from increasing arterial flow to the affected limb.

In the management of shock secondary to peripheral circulatory failure, the early administration of blood in adequate amounts (the ultimate volume trapped in the leg has been estimated at 4,000 ml. or more in some cases)[32] should be the initial treatment of choice. If the shock does not respond to replacement of fluid, Blum and Herman[18] have suggested ligation of the femoral artery to prevent further loss of fluid into the leg. Such a drastic procedure, which usually necessitates subsequent amputation of the leg at the level of the upper part of the thigh, can be considered as reasonable treatment only when it is clear that the life of the patient cannot be maintained by any other treatment.



**Summary and Conclusions**

Gangrene of the lower extremity caused by extensive venous occlusion is an uncommon entity. A study has been made of 11 such cases encountered at the Mayo Clinic during the 31-year period ending in 1959. Only one of the patients was alive at the time of the study.

Neoplastic disease was the most frequently observed underlying process in this series. Despite extensive venous occlusion, with involvement of the inferior vena cava in five cases, the renal vein was involved in only one. Peripheral circulatory failure with shock occurred in three patients and was a grave prognostic sign. The commonest cause of death was pulmonary embolism.

Complete obstruction to the venous return is probably the basic etiologic factor, but further study of the extremely small arteries and arterioles is necessary before the cause of this type of gangrene can be known with certainty.

The management of phlegmasia cerulea dolens and complicating peripheral circulatory failure is not satisfactory. Shock should be treated by the early use of blood.

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# Intermediate Coronary Syndrome

*By* RUSTOM JAL VAKIL, M.D.

SEVERE or intractable chest pain, associated with sweating, vomiting, precipitate fall of arterial blood pressure, fever, and evidence of shock or collapse, clearly indicates a diagnosis of acute myocardial infarction. In marked contrast is the entity of angina pectoris, with its paroxysms of chest pain after effort, typical radiation of pain into the arm, feeling of viselike constriction in the chest, and prompt response to rest and nitroglycerin.

Between these two major forms of coronary heart disease is a wide and ill-defined zone, made up of many heterogeneous groups, but with the common denominator of pain, usually intermediate in severity and duration between that of angina pectoris and acute myocardial infarction. Characterized typically by one or more bouts of prolonged chest pain, each lasting from 15 minutes to several hours, an equivocal or poor response to rest and nitrites, usually unrelated to physical effort, and, as a rule, unassociated with peripheral vascular collapse, congestive cardiac failure, pulmonary edema, sustained fever or auscultatory abnormalities, this intermediate form of coronary attack is seldom if ever accompanied by evidence of gross myocardial damage, such as high values of serum glutamic oxaloacetic transaminase and erythrocyte sedimentation rate, leukocytosis, and pathologic Q or QS patterns in the electrocardiogram.

In the past, an attack of this type was indiscriminately classified either with angina pectoris or with acute myocardial infarction and designated by various terms including the following: atypical or anomalous angina; severe angina; angina of rest; angina decubitus; angina major; false angina;[1] forme fruste or spasmodic angina; the prodromal, precursor, premonitory,[2-6] impending,[7-8] preliminary,[9] ischemic or formative phase of myocardial infarction; "infarction without infarction," "slight coronary attack,"[10] "subendocardial infarction," "premonitory period,"[2] or "ambulatory form" of myocardial infarction.[11]

Despite the contention of Yater and associates[12] that, since any given attack of angina on effort or rest may be the premonitor of a coronary attack, the "premonitory phase" of acute coronary occlusion is much too vague and intangible an entity to warrant attention, recent studies tend to confirm the existence and high incidence of a distinct entity, clinically intermediate between angina and acute infarction.[13-15] Attention was first directed to this type of pain as a distinct entity in 1937 by Sampson and Eliaser[7] and Feil.[9] Numerous small groups of cases of this type have been reported sporadically thereafter.

Since the terms coronary failure[14, 15] and coronary insufficiency[16-22] are equally applicable on theoretical grounds to the syndromes of angina pectoris and myocardial infarction, these also being examples of failure or insufficiency of the coronary circulation, and since the term "coronary insufficiency" has been used indiscriminately in the past to include a variety of different entities, there is obvious need for a more suitable designation. The term "intermediate coronary syndrome," recommended independently in 1951 by Graybiel[23] in the United States, and by Vakil[24-26] in India, has proved acceptable to many, emphasizing as it does the "intermediate" character of the syndrome.

Because of the great tendency for these attacks to turn into classical episodes of myocardial infarction, and with a view to encourage attempts at prophylaxis, the alternative designation of "prethrombotic syndrome"

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The Bhansali Memorial Oration of 1960, Bombay Medical Union, India.

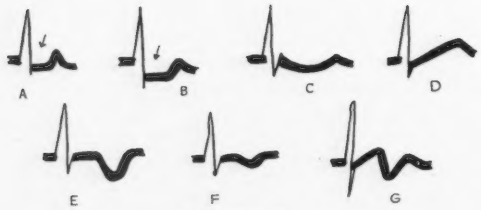


**Figure 1**

*Types of RS-T-T configurations encountered in intermediate coronary syndrome. A. Horizontal sagging (shallow depression of S-T). B. Deep horizontal sagging, (deep, "trough-like" depression). C. Curvilinear or crescent-shaped depression with downward "bowing" or convexity. D. Depression of S-T with obliquity upwards. E. Deep T-wave inversion. F. Shallow T-wave inversion. G. Coving of S-T segment with diphasic T wave.*


**Figure 2**

*Types of S-T depression not encountered, as a rule in myocardial ischemia. A. Curvilinear depression with upward bowing and symmetrically inverted T wave (common as reciprocal depression in infarction cases). B and C. Downward sloping or curvilinear S-T with upward bowing and asymmetrical T (in left ventricular hypertrophy or strain and intraventricular conduction defects). D. Straight RS-T directed obliquely downwards and merged with an asymmetrically inverted T (as in digitalis effect).*

was recommended,[24-26] in 1951, and has been accepted rather widely in the Eastern countries. However, since the intermediate coronary syndrome probably follows episodes of further coronary artery narrowing or occlusion, but precedes myocardial infarction, the term "preinfarction syndrome" may prove more acceptable to many.

Even the most obdurate and uncooperative patient, when forewarned of an impending attack of coronary thrombosis (by use of the prefix "prethrombotic" or "preinfarction"), is as a rule willing to accept any drastic restriction of activity or therapeutic regimen imposed by the physician. This term also alerts the physician in charge to the possibility of infarction in the near future. In a series of cases of coronary thrombosis, recently observed by the author,[26] the incidence of the "premonitory" syndrome of pain was 39 per cent. The high incidence, in the case of acute myocardial infarction, of a preliminary phase of chest pain antedating the infarction by days, weeks, or months, is now accepted universally on the basis of a well-founded body of evidence.[3, 25-27, 29] The importance of recognizing the entity lies in the prophylactic potentialities of early and appropriate therapy directed against imminent infarction.[2, 24, 25, 30] What is not sufficiently realized today is that the same syndrome of pain can arise in the course of any case of coronary atherosclerosis, with or without a history of angina or infarction, and may or may not develop into a classical attack of acute myocardial infarction. Studies by Blumgart and associates[31] on the effects of temporary occlusion of coronary arteries in animals have shown that the duration and severity of hypoxia of the myocardium are both important in determining whether the effects on the heart muscle shall be transient and reversible, as in the intermediate coronary syndrome or irreversible and associated with necrosis as in acute myocardial infarction.

The terms "intermediate," "prethrombotic," or "preinfarction" coronary syndrome, as used here, imply prolonged chest pain of cardiac origin, usually intermediate in intensity, duration, and character between that of angina pectoris and acute myocardial infarction, with a duration of from 15 minutes to several hours, bilateral or unilateral in distribution, with or without radiation, usually arising at rest, somewhat refractory to nitrite therapy, hardly ever associated with signs of shock, congestive heart failure, pulmonary edema, or gross myocardial necrosis (such as leukocytosis, high erythrocyte sedimentation rate, and serum glutamic oxaloacetic transaminase values,[32] and sustained pyrexia), almost invariably accompanied by electrocardiographic manifestations of myocardial ischemia, and terminating either in recovery or an attack of acute myocardial infarction.

Since the electrocardiographic signs of my-

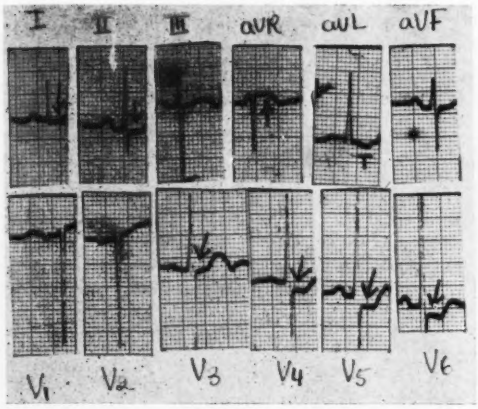


**Figure 3**

*Electrocardiograms of a 53-year-old man with hypertension and severe chest pain. Marked "horizontal sagging" or transverse depression of RS-T segments in leads I, II, $V_3$, $V_4$, $V_5$, and $V_6$. Anterolateral myocardial ischemia. High voltage of QRS in V leads suggest left ventricular hypertrophy. Another electrocardiogram 3 days later showed restoration of RS-T segments to isoelectric levels.*

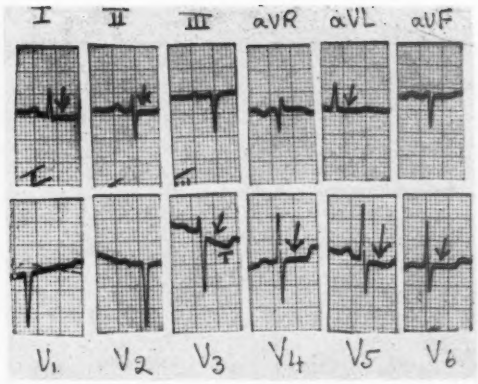


**Figure 4**

*Electrocardiograms of a 43-year-old woman, with diabetes and obesity. Severe chest pain of 3 hours' duration at the time of record. Shallow transverse depression of RS-T segments in leads I, II, $aV_L$, and $V_3$ to $V_6$ with left axis deviation and small T waves. Anterolateral myocardial ischemia. Complete clinical and electrocardiographic recovery within 12 hours.*

ocardial ischemia are usually observed best in the precordial leads, their recognition has been necessarily recent, after the routine introduction of Wilson's technic of extensive exploration of the anterior chest wall. The electrocardiographic signs of the syndrome, now fairly well defined, are usually of anterior wall myocardial ischemia. The present investigation is a correlation of clinical and electrocardiographic data in 251 personally observed cases of the "intermediate coronary syndrome." It attempts to investigate the incidence, clinical features, electrocardiographic manifestations, laboratory findings and clinical course in a fairly large and representative series of cases of the syndrome.

## Material and Method

The subjects of this study were 251 cases of intermediate coronary syndrome selected over a 10-year period from the author's consultative practice. Certain rigid criteria were carefully observed in their selection: (1) prolonged and characteristic chest pain of more than 15 minutes' duration; (2) absence of clinical, laboratory, and electrocardiographic evidence of gross myocardial necrosis (e.g., high or sustained pyrexia, leukocytosis, high serum glutamic oxaloacetic transaminase, high values of C-reactive protein or erythrocyte sedimentation rate, and Q or QS patterns in the electrocardiogram); (3) evidence of electrocardiographic signs of myocardial ischemia at some time during the course of illness; (4) availability of two or more 12- to 16-lead electrocardiograms during the period of observation; (5) a personal follow-up of each case of at least 3 months. Approximately 980 electrocardiographic tracings were examined in the study, and the period of follow-up ranged from 3 months to 10 years.

All doubtful cases, cases free of pain (even though associated with so-called "pain equivalents," such as dyspnea, vomiting, or exhaustion), patients with inadequate investigation or follow-up, and cases that failed to fulfill the aforementioned criteria, were excluded from the investigation. Thus, of 364 possible cases of the syndrome, only 251 were selected for study; the others proved to be cases of transmural infarction, acute pericarditis, rheumatic pancarditis, heart strain, pulmonary embolism, tobacco angina, hiatus hernia, gastrocardiac syndrome, psychoneurosis, and pheochromocytoma.

## Clinical Data

### Clinical Masquerades

Over 90 per cent of cases of the intermediate coronary syndrome had been incor-

**Table 1**

*Occupational Classification of 216 Male Cases of Intermediate Coronary Syndrome*

| | Occupational class | Case numbers |
|---|---|---|
| I | Executive or managerial | 49 |
| II | Professional (e.g., doctors) | 57 |
| III | Semi-professional (e.g., technicians) | 20 |
| IV | Skilled workers (e.g., armed forces) | 41 |
| V | Semi-skilled workers (e.g., mechanics) | 30 |
| VI | Unskilled workers (e.g., mill-hands) | 16 |
| VII | Unemployed | 3 |
| | | 216 |

rectly diagnosed at the outset as "severe angina," "status anginosus," acute myocardial infarction, myofibrositis of chest wall or shoulder, functional heart pain, gastrointestinal disorder, hiatus hernia, dry pleurisy, or cardiac insufficiency.

#### Incidence of Intermediate Coronary Syndrome

During the 10-year period 1946 to 1955, of the 1,804 cases of proved acute myocardial infarction treated by the author, 39 per cent gave a history of "premonitory" or "preinfarction" chest pain. These cases, however, not having been observed during the premonitory or preinfarction phase of pain, were excluded from the present study. The incidence of similar pain has been previously reported from 29 to 50 per cent.[6-8, 27] However, since most attacks of premonitory pain are not diagnosed at the outset and seldom are the subject of specialist attention, their incidence is probably much higher than is usually reported.

#### Composition of the Group

There were 251 cases of intermediate coronary syndrome, the average age was 55 years and the range was 27 to 81 years. Two hundred and sixteen were men, with an average age of 58 years. The ratio of male to female subjects was 6.2 to 1. There was a relative preponderance of men in younger age groups (43 men to three women under the age of 40 years), and of women after the age of 70 years (four women to 15 men). The immunity of young women to coronary artery disease has been commented upon by many authors.[33-35]

**Table 2**

*Incidence of Important Pre-existing Diseases in 251 cases of Intermediate Coronary Syndrome*

| Etiologic factors | Percentage |
|---|---|
| Hypertension | 36.8 |
| Angina pectoris | 50.4 |
| Obesity | 28.4 |
| Coronary occlusion | 5.2 |
| Gallbladder disease | 4.0 |
| Diabetes mellitus | 13.6 |

#### Family History

Dependable information about parental health was obtainable in 182 cases, a history of coronary heart disease in one or both parents was present in 22 per cent. In a comparative series of 200 normal subjects free of coronary disease, the parental incidence of coronary disease was 6 per cent.

#### Racial Incidence

In view of the gross inequality of representation of various racial groups in the author's consultative practice, a correct appraisal of this factor was considered not possible and was abandoned.

#### Occupational Factors

The relatively higher incidence of coronary disease in executive and professional classes, as noted previously,[12, 35] was confirmed in this series (table 1).

#### Pre-existing Conditions

Evidence of past hypertension, previous attacks of myocardial infarction, angina pectoris, and noncardiac ailments was frequent (table 2).

Precipitating factors were frequent, though less frequent and less well defined than in the case of acute myocardial infarction.[25, 26] Of the numerous factors incriminated, the most important were excessive or unusual physical or mental activity, overeating, long journeys, acute hemorrhages, and drugs (particularly insulin and ganglion-blocking agents).

#### Clinical Analysis of Pain

Of the numerous symptoms reported, the most constant by far was that of pain, which was noted in every case. Although attacks of preinfarction syndrome free of pain are theo-

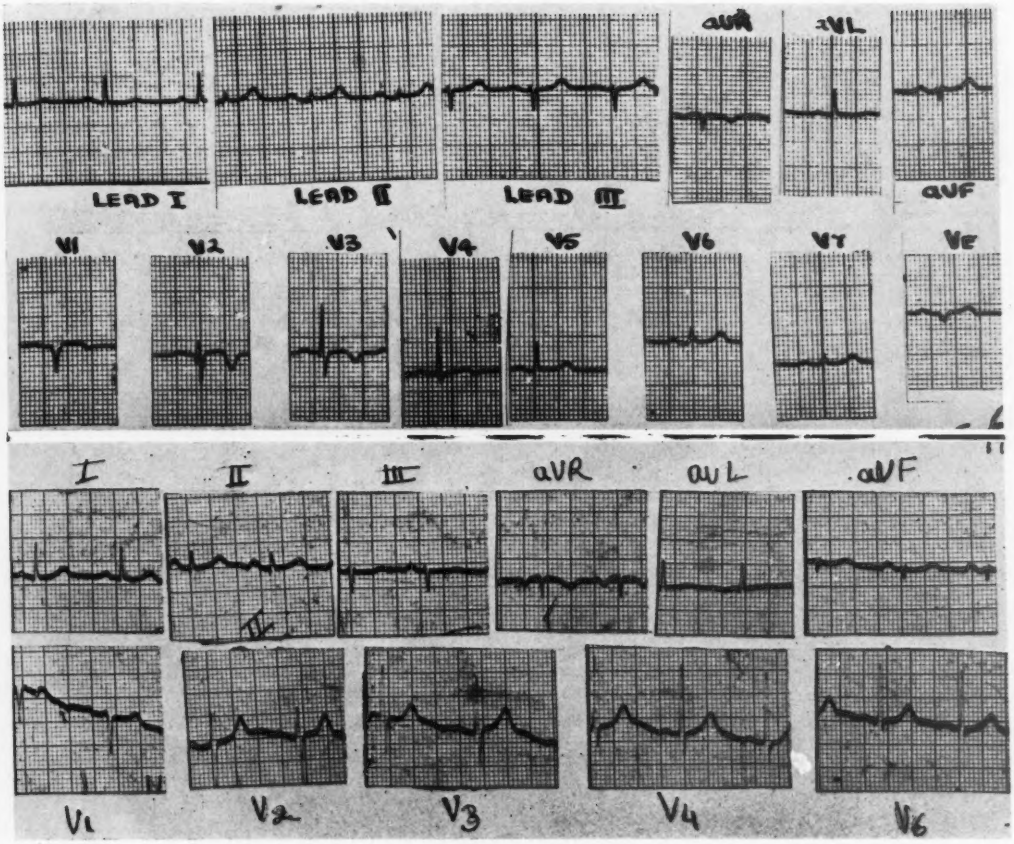


**Figure 5**

*Electrocardiogram of a 34-year-old man with chronic cholecystitis and obesity. Severe aching of left arm on and off for 3 days before examination.* Top. *Deep T-wave inversions in leads $V_1$, $V_2$, and $V_3$ as isolated abnormalities. Septal localization of myocardial ischemia.* Bottom. *Electrocardiogram, 3 days later, shows return to normal patterns.*

retically possible, an analytical study of pain is proverbially difficult because of the great effect of drugs given by the attending physician.

**Site of Pain**

In over 65 per cent of cases, the pain was located in the center of the chest, either retrosternally or just to the left or right of the sternum. In 9 per cent, it was reported as diffuse and bilateral, and in 5 per cent as precordial or left mammary. In the remaining 24 per cent, the pain was located anomalously, either in the back, epigastrium, shoulder, arm, elbow, or wrist (usually left) or both arms, lower jaw, neck, tongue, or ear. In one case the pain was confined to the back of the tongue, throughout successive episodes of angina pectoris, intermediate coronary syndrome, and myocardial infarction.

**Radiation of Pain**

The intermediate coronary syndrome showed radiation of pain in 45 per cent of cases, which was less frequent and less diffuse than in myocardial infarction. Radiation to both arms or shoulders was observed in 24 per cent, to the left arm in 13 per cent, right

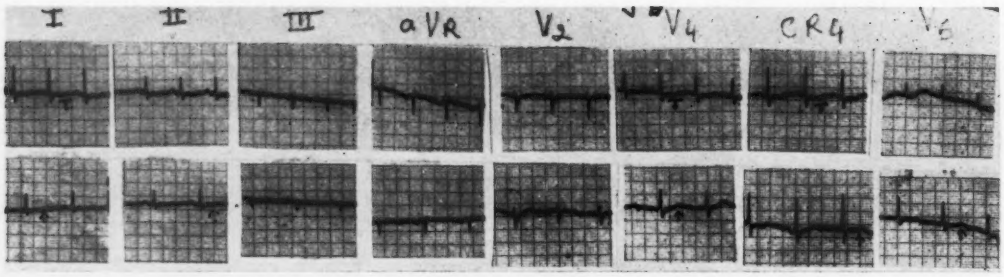


**Figure 6**

*Electrocardiogram of a 46-year old man with intense, bilateral chest pain.* Top. *Electrocardiogram during attack of pain shows shallow inversions of T waves in lads I, II, $V_4$, $CR_4$, and $V_6$ with left axis deviation. Anterolateral distribution of myocardial ischemia.* Bottom. *Electrocardiogram, taken 4 days later, shows return of T waves to normal.*

arm in 4 per cent, epigastrium in 7 per cent, back in 9 per cent, and lower jaw or throat in 4 per cent.

**Types of Pain**

Although many types of chest pain were described by patients, they were grouped in three main types: "angina-like" pain, "infarction-like" pain, and "anomalous" or "ill-defined" pain. The angina-like pain, particularly common in those with a history of past angina, was similar to that of classical angina but showed longer duration (from 15 minutes to 2 hours), greater intensity, wider radiation, atypical character (aching, burning, or lancinating), greater frequency, tendency to arise during rest or sleep and little or no response to nitrites.

The infarction-like pain, was comparatively much more prolonged, less frequent, occurred during exercise or rest, was frequently referred to both arms, back, or epigastrium, displayed a "crescendo" character, and was usually described as "weight-like," "vice-like," "crushing," or "boring," in character. More than three bouts of this type of pain were not observed in any case. In some of the more severe cases, repetitive bouts of angina-like pain were associated with one or two bouts of more prolonged infarction-like pain.

The anomalous or ill-defined type of pain was readily recognized when it was associated with one of the more characteristic types of pain; when it occurred alone, it proved a source of great diagnostic confusion. It was described as a precordial ache or oppression (at times associated with local tenderness), a sharp and repetitive pricking pain in the left mammary or inframammary region, a persistent heart burn, an ache in the shoulder or wrist, or a high interscapular pain. For days, at times, the pain was dismissed as neurotic or osteoarthritic in origin. The crescendo character[27] and aching or burning nature of the premonitory pain[36] were confirmed in a fair percentage of cases.

**Number of Attacks of Pain**

The number of attacks of chest pains was extremely variable, ranging from one solitary bout of prolonged pain to over 250 paroxysms of angina-like pain. In some, angina-like pains of increasing severity, duration, and frequency were observed for days at a time, with a final, severe, and prolonged bout of infarction-like pain lasting from 4 to 40 hours.

**Relieving Factors**

Although the response to nitroglycerin or analgesic tablets was poor in most cases, a minor degree of relief was sometimes experienced after these measures. In the great majority, relief occurred either spontaneously or after the parental administration of an opiate.

**Accompanying Symptoms**

Associated with pain in the chest were many other symptoms, the most frequent being fatigue or exhaustion, dyspnea, palpita-

tion, aching of the arm, backache, epigastric discomfort, missing of beats, aerophagy or excessive flatulence, nausea, dizziness, "choking," peripheral sensory manifestations (such as tingling or "pins and needles"), vomiting, and sweating.

### Physical Findings

Clinical examination of the heart, even at the height of pain, was surprisingly devoid of abnormal signs. Apart from frequent disturbances of cardiac rate and rhythm, occasional low-grade systolic murmurs at the base or apex, and rare instances of "bruit de gallop," there were no signs of heart disease. Initial rises of blood pressure, of from 10 to 90 mm. Hg systolic and 5 to 40 mm. diastolic, were observed during the bouts of pain in the majority of cases, later to be followed by normal or somewhat low levels. In some cases, paradoxical falls of blood pressure (systolic, diastolic, or both) of from 5 to 50 mm. systolic and 5 to 20 mm. diastolic were noted from the very outset of pain. The highest pressures recorded in the present series were 228 mm. systolic and 130 mm. diastolic. Mild rises of body temperature of 1 to 2 F. and lasting for 1 to 6 days were noted in about 12 per cent of cases. No examples of sustained or high pyrexia were encountered except for one case in which fever of over 103 F. for 2 or 3 days resulted from an upper respiratory virus infection.

### Laboratory Findings

The total and differential white blood counts were normal in 72 per cent of cases. The remainder showed slight leukocytosis (usually less than 9,500 cells). The erythrocyte sedimentation rate, usually normal, was raised slightly (20 to 35 mm. at the end of 1 hour) in 23 per cent; and the C-reactive protein content was elevated (1 or 2 plus) in 20 per cent of cases. Of 52 cases, in which the serum glutamic oxaloacetic transaminase value[32] was estimated, 33 showed values below 40; the remainder, values of from 40 to 79. The laboratory findings were of value in ruling out gross degrees of myocardial necrosis or damage.

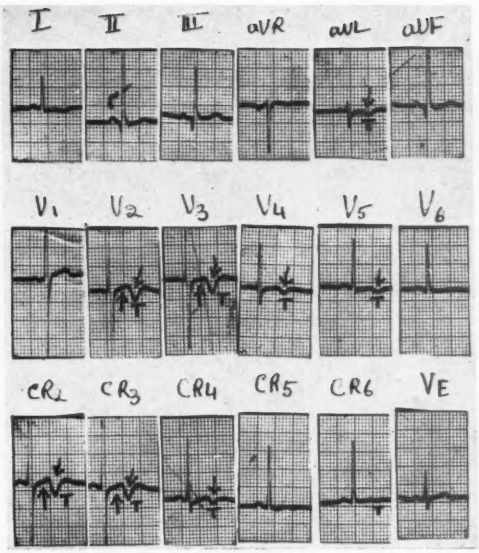


**Figure 7**

*Electrocardiograms of a 59-year old man with long-standing hypertension and angina pectoris. Electrocardiograms, at the time of pain, show characteristic "coving" of RS-T segments with diphasic or inverted T waves in leads $V_2$ and $V_3$. Deep and shallow inversions of T waves also observed in leads $V_4$, $V_5$, and $aV_L$. The electrocardiogram is suggestive of anterior wall ischemia. The electrocardiogram is suggestive of anterior wall ischemia. Typical attack of anteroseptal myocardial infarction, supervened after 3 weeks of the preliminary pain.*

### Fluoroscopy of the Heart

Of 86 cases subjected to fluoroscopy, 52 had normal-sized hearts, whereas 32 displayed early left ventricular hypertrophy.

### Clinical Course

The clinical course was uneventful in most cases, complete recovery usually following one or more bouts of severe chest pain. In 93 of the cases, acute myocardial infarction developed within 3 months of the premonitory attack of pain. Two patients died during the acute episode, one from sudden death on the second day (presumably from ventricular fibrillation, having displayed multifocal ventricular extrasystoles a day earlier) and one from acute pulmonary edema on the third day of illness. Serious pulmonary, cerebro-

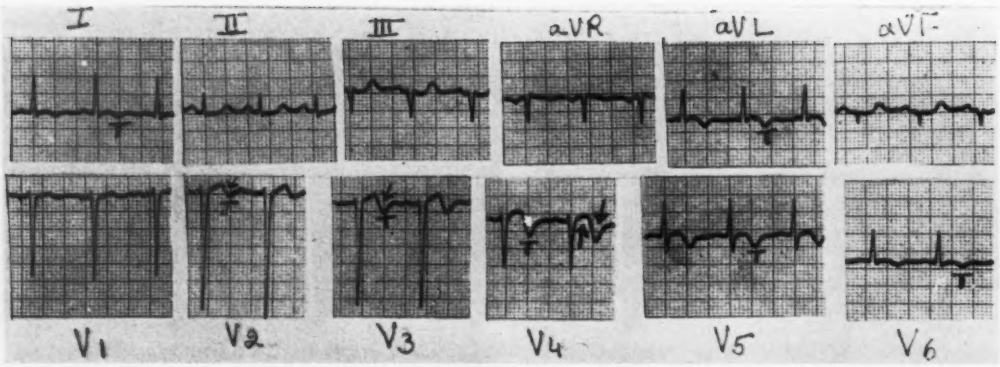


**Figure 8**

*Electrocardiogram of a 68-year-old man with hypertension (200/120), obesity, and anginal pains. Record, taken during a prolonged bout of anginal pain, shows coving of RS-T segments with diphasic T waves in leads $V_2$, $V_3$, and $V_4$, sharp and deep inversions of Tin $aV_L$ and $V_5$, and shallow inversions of T in lead I and $V_6$. Two months later, patient had a more severe bout of pain, resulting in an extensive anterior wall myocardial infarct.*

vascular, embolic, and peripheral vascular complications were not observed in any cases. Peripheral failure or shock, with sudden drop of blood pressure, thready pulse, and cold and clammy extremities, were not observed in the entire series. Attacks of angina pectoris were experienced by 40 per cent of the patients, even after subsidence of acute episodes of premonitory pain.

### Electrocardiographic Data

Despite a massive literature on the subject of electrocardiographic manifestations of coronary insufficiency, there is little unanimity of opinion[37-51] regarding the incidence or nature of abnormalities. Electrocardiographic abnormalities, suggestive of myocardial ischemia were noted in every case of the present series, over 900 electrocardiograms having been recorded during the period of observation. It has been our experience that electrocardiographic signs of myocardial anoxia are always present in such cases, provided 12 to 16 leads are recorded during or just after the painful episodes. The absence of electrocardiographic abnormalities reported in earlier series may be due either to lack of serial electrocardiographic study or improper exploration of the anterior chest wall. Besides standard chest leads, high anterior and posterior leads were frequently necessary in doubtful cases. Electrocardiographic manifestations of myocardial ischemia may either antedate or form an integral part of the early phase of an acute myocardial infarction.

The electrocardiographic picture of intermediate coronary syndrome, although apparently similar to that of fresh myocardial infarction, is usually distinguishable by the following points: (1) the entire sequence of events or "temporal course of evolution" is far more rapid, being a matter of hours or days rather than weeks or months; (2) lack of involvement of the QRS complex; (3) lack of reciprocal changes in the ST-T segments, with most leads showing downward displacement.

#### Characteristic ST-T Patterns

Certain characteristic types of ST-T complex configuration were observed (either singly or in combination) in every case of the present series (figs. 1 to 12).

*Type I*

A horizontal trough-like depression or sagging of the RS-T segment, deep or shallow, was observed in over 92 per cent of all records (figs. 1*A* and *B*) and was frequently associated with an upright and symmetrical, short or tall, peaked T wave and a deep S

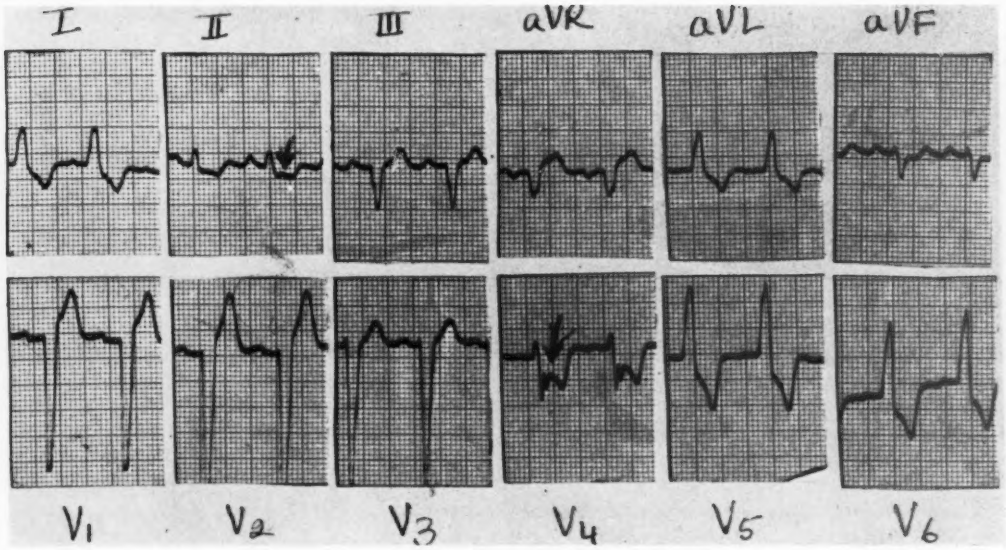


**Figure 9**

*Electrocardiograms of a 58-year-old man with chronic hypertension and obesity. Record taken during an attack of prolonged chest pain, shows in addition to a pattern of left bundle-branch block, marked horizontal "sagging" or depression of the RS-T segment, particularly in leads $V_4$ and II. After subsidence of pain, the RS-T segments returned to original levels.*

wave. At times, the S-T depression showed an obliquity upwards (fig. 1*D*) or a curvilinear or crescent shape with downward convexity (fig. 1*C*). Depression of S-T segments was particularly frequent in leads I, II, $aV_L$, and $V_4$ through $V_6$ (fig. 3).

The S-T depression was seldom accompanied by reciprocal S-T elevation, as in the case of acute myocardial infarction, except when associated with left ventricular hypertrophy, left-sided heart strain, or bundle-branch block.

*Type II*

Isolated T wave negativity (fig. 1*E* and *F*), Inversion of the T wave in one or more leads, usually of the midprecordial series ($V_2$, $V_3$, and $V_4$), was encountered in 40 per cent of cases. Such changes have already been described as evidence of local myocardial ischemia[37, 39, 46, 49] Transitory inversion of the T wave, whether deep or shallow, was usually confined to one to three leads but occasionally was diffuse enough to appear in most leads. Other noteworthy features of this type of tracing (fig. 7) were no displacement of the S-T segment and a symmetrical configuration of the T wave with a peaked apex and rounded shoulders. The degree of T-wave inversion often varied from time to time, even in the same case.

T-wave negativity does not necessarily imply myocardial ischemia unless it is transitory and associated with confirmatory symptoms and signs. Persistent or progressively increasing negativity of the T wave, besides being a rare physiologic variant, may be indicative of myocardial infarction.

*Type III*

Coving of RS-T segment with diphasic or inverted T wave (fig. 1*A*). Somewhat similar to early ST-T configuration of classical myocardial infarction, this type of electrocardiographic pattern was encountered as a transitory event in 12 per cent of cases, the lead most frequently affected being the midprecordial lead $V_3$ (fig. 7). The complex usually displayed a high take-off with prominent coving or upward convexity of the RS-T segment and

**Table 3**

*Localization of Myocardial Ischemia in 251 Cases of Intermediate Coronary Syndrome*

| | Localization | Leads involved | Case numbers | Percentage incidence |
|---|---|---|---|---|
| 1 | Anterolateral | $V_4$ to $V_6$, I, $aV_L$, and high V leads | 65 | 26 |
| 2 | Anteroseptal | $V_1$ to $V_3$ and $V_E$ | 24 | 9.6 |
| 3 | Extensive anterior wall | $V_1$ to $V_6$, I, $aV_L$, VE, and high V leads | 37 | 14.8 |
| 4 | High anterolateral | I, $aV_L$, and high V leads | 8 | 3.2 |
| 5 | Localized anterior or anteroapical | $V_3$ and $V_4$ | 14 | 5.6 |
| 6 | Posterior wall | II, III, $aV_F$, and Oe* | 12 | 4.8 |
| 7 | Posterolateral | II, III, $aV_F$, $V_5$, $V_6$, and Oe* | 15 | 6 |
| 8 | Posteroseptal or posteroinferior | II, III, $aV_F$, VE and Oe* | 12 | 4.8 |
| 9 | High posterolateral | I; $aV_L$, V''6 to V''9 | 2 | 0.8 |
| 10 | Global or diffuse (anterior and posterior wall) | I, II, III, $aV_L$, $aV_F$, $V_1$ to $V_6$ | 23 | 9.2 |
| 11 | Successive anterior and posterior or vice versa | —— | 11 | 4.4 |
| 12 | Miscellaneous and indeterminate forms | —— | 28 | 11.2 |

*Esophageal leads.

**Table 4**

*Frequency of Electrocardiographically Observed Arrhythmias in 251 cases of Intermediate Coronary Syndrome (980 Electrocardiographic Records)*

| | Number of cases | | Number of cases |
|---|---|---|---|
| Sinus tachycardia | 57 | Atrial fibrillation | 3 |
| Sinus bradycardia | 9 | Flutter fibrillation | 1 |
| A-V nodal rhythm | 2 | S-A block | 1 |
| A-V nodal escape | 2 | A-V block | 10 |
| Wandering pacemaker | 1 | First degree 8 cases | |
| Premature systoles | 44 | Partial or complete 2 cases | |
| Atrial 5 cases | | Intraventricular conduction defects | 14 |
| Nodal 3 cases | | | |
| Ventricular 36 cases | | | |
| Paroxysmal tachycardia | 3 | Right bundle-branch block 8 cases | |
| Supraventricular 3 | | Left bundle-branch block 2 cases | |
| Ventricular 0 | | Arborization block 4 cases | |

a large, diphasic or inverted T wave. The transitory nature of the abnormality, absence of associated QRS involvement, and lack of reciprocal ST-T segment changes are usually sufficient to rule out acute myocardial infarction and to suggest myocardial ischemia instead.

**Associated Findings**

Some of the records also showed abnormalities of the QRS complex, such as prominent S wave, small or absent R waves (particularly in the right precordial leads), and rarely pathologic Q waves in one or two of the anterior or posterior leads.[10]

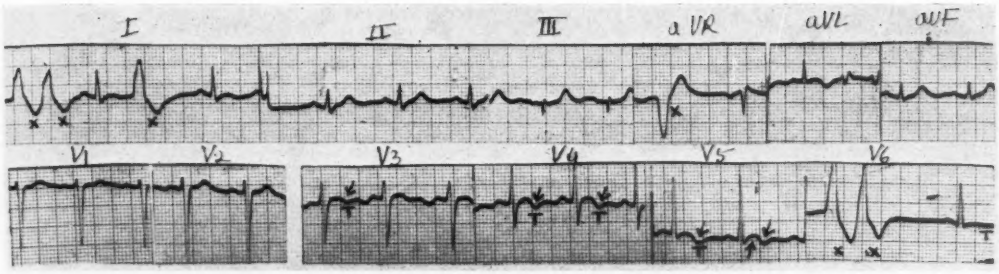


**Figure 10**

*Electrocardiograms of 51-year-old man, with severe chest pain and multiple extrasystoles. Isolated inversions of T waves are observed in leads $aV_L$, $V_3$, $V_4$, $V_5$, and $V_6$ with curvilinear RS-T segments. Same case, after 4 days, showed a high anterolateral myocardial infarction on electrocardiography.*

#### Differential Diagnosis

Nonspecific abnormalities[48] of the ST-T complex, may be due to causes other than myocardial ischemia, such as ventricular strain, intraventricular block, digitalis effect, and thyrotoxicosis[52] (fig. 2). The characteristic features of each type of S-T depression, however, usually permit differentiation of the different varieties. In ventricular strain or intraventricular block, the ST-T complex is usually displaced opposite to the main QRS deflection, the RS-T segment is bowed or convex upwards whenever it is depressed, and the two limbs of the T wave are unequal or asymmetrical. In case of digitalis effect, the S-T depression displays a downward slope and the T wave is grossly asymmetrical, with a long downstroke and a short upstroke. In thyrotoxicosis, besides horizontal sagging of the RS-T segment, there are present marked depression of the P-R segment, tall P waves and sinus tachycardia.[52] In contrast, the S-T depression of intermediate coronary syndrome is usually deeper, wider, more horizontal, and trough-like, and the T wave is peaked or pointed, symmetrical, and directed upwards, in a direction opposite to the S-T segment.

#### Localization of Myocardial Ischemia

Although infarction of the anterior wall is somewhat commoner than that of the posterior wall, the relative incidence of anterior wall ischemia (to posterior wall ischemia) is even higher.[51, 53] On the basis of distribution of ST-T abnormalities, the localization of myocardial ischemia was delineated (table 3): anterior wall ischemia (148 cases) was observed about 3.5 times as frequently as posterior wall ischemia (41 cases) in the present series.

#### Cardiac Arrhythmias

Besides the characteristic ST-T patterns of myocardial ischemia, transitory or persistent abnormalities of cardiac rate, rhythm, or conduction were also observed in some cases (table 4).

#### Stabilization of Electrocardiogram

A complete restoration of the electrocardiographic patterns to normal was observed in 98 cases, the restoration being effected in less than 24 hours in 18 cases, in 1 to 7 days in 38 cases, 1 to 4 weeks in 34 cases, and 1 to 3 months in eight cases, the average for the whole group being 7 days. In some of the cases, there were recurrences of myocardial ischemia with recurrent bouts of chest pain. In those cases in which acute myocardial infarction supervened, the electrocardiographic pattern of ischemia changed to one of infarction, either directly or more often after a normal phase.

### Discussion

Recent work suggests that the syndrome is "at least half as common as acute transmural myocardial infarction"[53] and represents the "third most important category of coronary heart disease," being next in importance only to coronary thrombosis and angina pectoris.

The pathogenesis of the syndrome is also

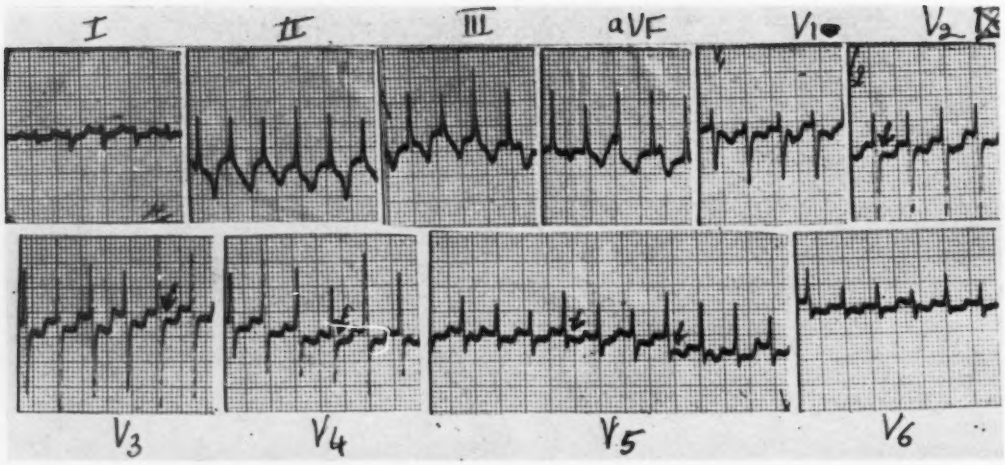


**Figure 11**

*Electrocardiogram of a 38-year-old man with typical intermediate coronary syndrome. The record, taken at the height of pain, shows paroxysmal supraventricular tachycardia with depression of RS-T segments in anterior and posterior wall leads. Eighteen days later, the patient had a typical attack of myocardial infarction with posterior wall myocardial damage.*

far from clear. According to Mounsey,[27] the prodromal pain of myocardial infarction is due to the "gradually decreasing lumen of a coronary artery," irrespective of the nature of the occlusive process. Papp and Smith[10] regarded "small intramural or patchy subepicardial infarctions" as likely causes of "slight coronary attacks." The average of two or more occlusions in the main branches of the coronary arteries, as demonstrated by Blumgart et al.[13] in cases of angina pectoris, has revolutionized our concepts of coronary artery disease. On the basis of their work, it would be reasonable to assume the existence of similar, silent occlusions of the coronary vessels in cases of the intermediate coronary syndrome.

The entity of subendocardial infarction[41] has assumed great importance in recent years, thanks to the widespread employment of unipolar chest leads. Recent studies confirm the existence of myocardial infarcts localized to the subendocardial layers of the myocardium (much less common than transmural infarcts) secondary to coronary occlusion or acute coronary insufficiency, and associated with persistent and characteristic depressions of the ST-T complex without involvement of QRS. Of the many cases of "myocardial infarction without acute coronary occlusion" or "non-occlusive acute coronary insufficiency with infarction," studied by Miller et al.,[54] 82 per cent were subendocardial. In another group of myocardial infarctions, the incidence of subendocardial infarctions was only 11 per cent.[54]

Among the pathogenetic mechanisms suggested for the intermediate coronary syndrome are partial or complete occlusion of a coronary vessel by a thrombus, subintimal hemorrhage, atheromatous plaque, scar, or vasospasm.

In this era of scientific electrocardiography, when practically all electrocardiographic phenomena are explainable in terms of physical or physiochemical theory, the erratic or aberrant behavior of the ST-T complex continues to offer a challenge. Similar abnormalities of the S-T segment or T wave may be noted under widely dissimilar circumstances as in acute or chronic coronary insufficiency, subendocardial infarction, myocarditis, digitalis effect, ventricular strain, and intraventricular conduction defect.[52] While one patient

with marked RS-T depression or inverted T wave may be completely symptomless, another with an identical tracing may be moribund.

The causes of S-T depression are many. Depression of the segment may be either spontaneous or induced after exercise or anoxemia. The former may be evanescent as in angina pectoris, transitory as in acute coronary insufficiency, or persistent as in subendocardial or intramural infarction, early phase of transmural infarction, ventricular strain, or intraventricular conduction defect. Prolonged depression of RS-T segment without involvement of QRS, even when of coronary origin, may mean either an acute coronary insufficiency without infarction, a subendocardial or intramural infarct, or the early stage of evolution of a transmural infarct. The clinical picture in conjunction with the electrocardiographic tracing and a short-term follow-up frequently provides the desired clue for diagnosis.

Differential diagnosis of the intermediate coronary syndrome from angina pectoris or coronary thrombosis frequently requires a close observation of the patient for 7 to 10 days, with dependence on a careful history, serial electrocardiographic exploration, and repeated examinations of the blood. A correct diagnosis often depends on a correct appraisal of the various characteristics of the syndrome:[13-15] (1) pain, usually intermediate between that of angina and myocardial infarction; (2) little or no alteration of blood pressure; (3) absence of clinical, laboratory, and electrocardiographic signs of myocardial necrosis; (4) absence of shock, embolization, and cardiac decompensation; (5) characteristic S-T depression or T-wave inversion without reciprocal elevation; (6) evidence of myocardial ischemia (usually) of the anterior heart wall; and (7) an uncomplicated recovery as a rule but with a subsequent tendency to infarction.

Regarding prognosis, most reports justify an outlook of optimism. In the present series, there were two deaths, one presumably from ventricular fibrillation and the other from acute pulmonary edema. Apart from an occasional fatality, therefore, the immediate outlook of cases of this syndrome can be regarded as good, provided acute myocardial infarction does not supervene sooner or later, as in 91 of the 251 cases of the present series, who developed infarction within 3 months of onset of preliminary pain. The role of rest and anticoagulant therapy as prophylactic agents against infarction, forms the subject of another study.

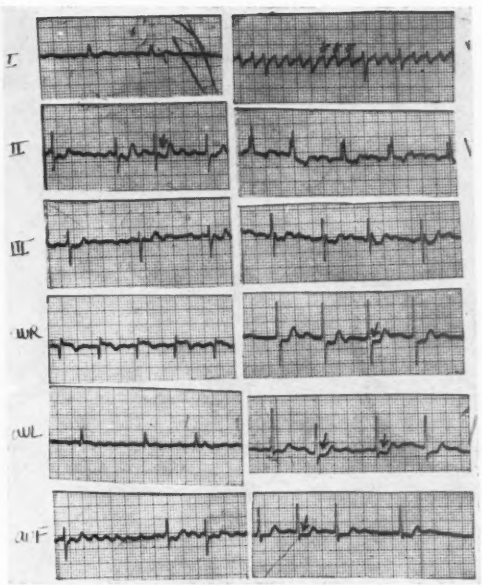


**Figure 12**

*Electrocardiograms of a 48-year old diabetic man, with generalized arteriosclerosis, intermittent claudication and attacks of angina of rest. Record during a bout of pain shows RS-T segment depressions in anterior wall leads with atrial flutter-fibrillation. Later records showed persistence of the old-standing arrhythmia, but without the RS-T segment depression.*

### Summary and Conclusions

A clinical material of 251 cases of the "intermediate," "preinfarction," or "prethrombotic" "coronary syndrome" diagnosed on the basis of certain well-defined criteria and observed in consultative practice, forms the subject matter of this paper.

Each case was subjected to clinical, laboratory, and electrocardiographic investigation. Most of the cases had "infarction-like" or "angina-like" pains of moderate severity, in-

significant alterations of pulse rate and blood pressure, little or no rise of temperature, and no evidence of shock, congestive cardiac failure, or gross myocardial necrosis. Characteristic electrocardiographic patterns of myocardial ischemia were observed in all cases. Ninety-one of the cases developed acute myocardial infarction within 3 months of the initial attack of pain.

Of the 980 electrocardiograms, recorded during the course of the investigation, the great majority showed either markedly depressed, "trough-like" S-T segments, isolated deep or shallow inversions of T waves, or "coving" of S-T segments with diphasic or inverted T waves. Anterior wall involvement (particularly of anterolateral type) was encountered far more often than posterior. Electrocardiographic restoration to normal was prompt and complete in most instances.

On the basis of this study, the intermediate coronary syndrome appears to be a fairly common, recognizable clinical entity, usually self-limited but with a proclivity to develop acute myocardial infarction in the near future.

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# The Influence of the Ventriculotomy Site on the Contraction and Function of the Right Ventricle

*By* HAROLD W. MARCH, M.D., J. KEITH ROSS, F.R.C.S., WILLIAM L. WEIRICH, M.D., AND FRANK GERBODE, M.D.

EXPERIENCES in the surgical research laboratory and in the operating room have served to refine the technic of open cardiotomy for the repair and correction of anomalies involving the ventricular septum, the right ventricular outflow tract, and the pulmonary valve. These refinements have been reflected in a steadily declining mortality following the repair of ventricular septal defects and the correction of Fallot's tetralogy.[1, 2]

There remains, however, a group of patients with these lesions in whom surgery continues to be hazardous. In this group right ventricular pressures are high preoperatively and right ventricular work burden remains increased postoperatively. This includes patients with ventricular septal defects in whom the pulmonary artery pressure preoperatively was 70 per cent or more of the systemic pressure, particularly when this was associated with high pulmonary vascular resistance.[3] It embraces some of those with Fallot's tetralogy in whom, because of incomplete relief of outflow tract obstruction, the right ventricular pressure remains elevated.[4] And, finally, there should be included certain patients who had incomplete repairs of ventricular septal defects in association with infundibular stenosis.[5]

One factor that these patients have in common is the persistence postoperatively of increased right ventricular work loads. Clinical observations and physiologic considerations suggest that postoperative morbidity and death may be a consequence of impaired right ventricular functional capacity. Since right ventricular failure in untreated cases is a late event, and is rare preoperatively, it would seem likely that the factor causing failure is acutely imposed and that it appears somewhere in the course of surgical intervention. Previous studies have shown that cardiac bypass with the pump oxygenator of itself does not cause a significant decrement of ventricular function in animals if the perfusion rate is kept at adequate levels, above 0.3 liters per minute per square meter or between 30 to 50 milliliters per kilogram per minute.[6] Although it has been established that both potassium and acetylcholine arrest of the heart result in pronounced depression of ventricular function,[7] operating-room experience had already indicated that these drugs are undesirable expedients and their use has been abandoned in many centers. They have been superseded by general body hypothermia or local cardiac cooling. Recent studies indicate that when hypothermia is effectively induced, so that temperatures are lowered sufficiently to produce and maintain cardiac standstill, no depression in ventricular function eventuates upon warming and restarting the heart.[8] On the whole, it seems unlikely that any of the foregoing aspects of open cardiotomy are currently responsible for impairment of right ventricular function. Nor are the details of postoperative care likely to be of great relevance in view of the fastidious care that distinguishes the management of these patients.

On the other hand, certain considerations involving the ventriculotomy procedure itself indicated that an investigation into the effects of right ventricular cardiotomy might be fruitful. This communication reports the ob-

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servations made in acute and chronic experiments in dogs by means of high-speed cinematography and ventricular function curves.

### Methods

Fourteen healthy mongrel dogs weighing from 15 to 21 Kg. were anesthetized with sodium pentobarbital, and respiration was mechanically supported on a respirator after endotracheal intubation. In most of the animals the thoracotomy incision extended across the chest, and the sternum was transected in order to provide adequate exposure of the right ventricle for photography.

In eight of the animals, conventional vertical ventriculotomies were made from base to apex paralleling the interventricular groove. In six of the animals ventriculotomies were oriented horizontally from the atrioventricular groove across the ventricle to a terminus at the interventricular septum, and roughly parallel to the plane of the pulmonic valve ring. Four of the animals with vertical ventriculotomies were restudied 2½ to 3 months after recovery from the thoracotomy procedure.

The cinefilms were made by a technic to be described fully elsewhere.[9] The camera was a 16-mm. Wollensak-Fastax run at frame rates of 800 to 1250 per second. The camera has a double-lens system permitting the superimposition on the film of any oscilloscopic signal. Superanscochrome daylight film was used, and illumination was provided by a high-intensity quartz lamp. The heat level from the lamp was low, and no damage to tissues was noted. Because of the high frame rates and the technical difficulties in reproducing long 16-mm. film strips with clarity, the cinefilm observations are presented by composite drawings of the pertinent portions of the cardiac cycle as derived from direct tracings of individual film frames.

Eight vertical and six transverse ventriculotomies were done in 14 additional animals in order to study the effects of these incisions by means of ventricular function curves constructed in the manner described by Sarnoff and Berglund[10] and Stirling and associates.[11] Ventriculotomy was performed under cardiopulmonary bypass with a pump oxygenator of recent design.[12] For the purpose of constructing right ventricular function curves, preventriculotomy and postventriculotomy, blood from the venae cavae cannulae was pumped back into the right atrium via the azygos vein over a suitable range of flows, 0.9 to 3.8 liters per minute per square meter. Heart rate and mean right atrial and pulmonary artery pressures were continuously monitored. The curves were constructed by plotting right ventricular stroke work in gram-meters against mean right atrial pressure in centimeters of water.

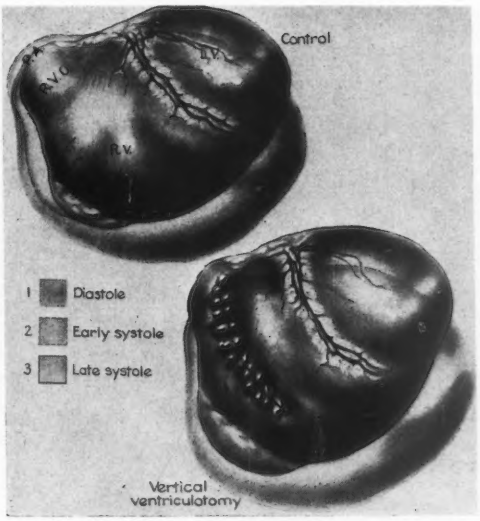


**Figure 1**

*Vertical ventriculotomy. R.V., right ventricle; R.V.O., right ventricular outflow tract; P.A., pulmonary artery; L.V., left ventricle. In the control study the R.V.O. bulges in early systole, moving concordantly with the P.A. In late systole the outflow tract is maximally contracted. A transverse depression marks the boundary between R.V. and R.V.O. After vertical ventriculotomy the R.V.O. bulge persists throughout systole. Note the almost complete lack of late systolic border motion. In addition there is paradoxical movement in the immediate vicinity of the ventriculotomy and the R.V.O. is not well delineated from the R.V.*

### Results

Cinefilm observations in the control animals indicate that right ventricular contraction is sequential, beginning at the apex. Early in systole the outflow tract bulges as blood is ejected into the pulmonary artery. It is maximally contracted late in systole and appears to relax later than the main right ventricular chamber. The preventriculotomy drawings in figures 1 and 2 illustrate the systolic events described.

In the eight animals undergoing conventional vertical ventriculotomy paralleling the interventricular groove, adverse effects on the mobility of the entire right ventricle and on

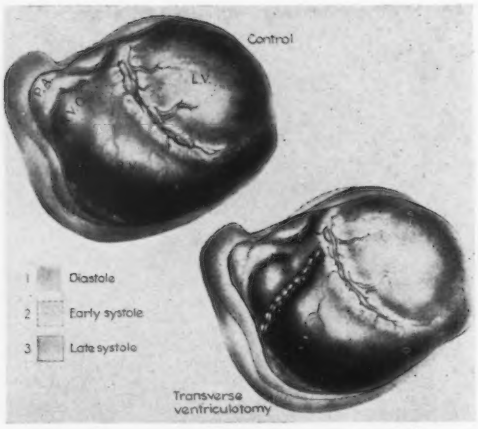


**Figure 2**

*Transverse ventriculotomy: R.V., right ventricle; R.V.O., right ventricular outflow tract; P.A., pulmonary artery; L.V., left ventricle. The transverse ventriculotomy extends from the A-V groove to the interventricular sulcus. There is no significant change compared with the control. The R.V.O. movement in late systole remains normal, and this segment is well delineated from the R.V. There is no paradoxical movement at the incision site.*

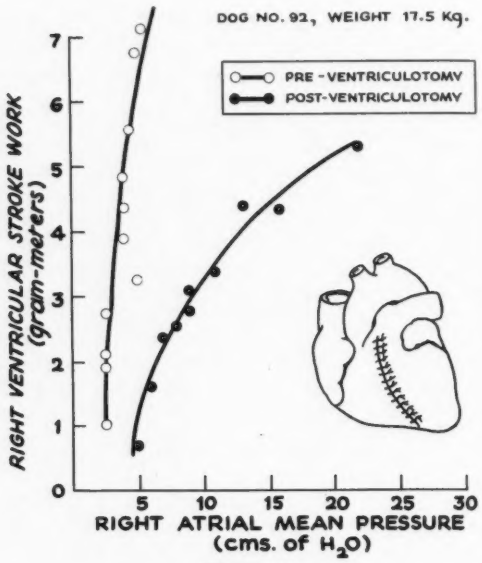


**Figure 3**

*Ventricular function curves before and after a long vertical right ventriculotomy. The stroke work was calculated over a range of flows, 1.1 to 3.2 L./min./M.². The curve is sharply depressed after ventriculotomy.*

the behavior of the outflow region were observed. The sequential pattern of contraction was either absent or markedly altered, and the final phase of ejection in the outflow tract appeared to occur passively. The area of the incision tended to move paradoxically. The outflow tract in most instances continued to bulge throughout systole and late contraction did not occur. In fact little change in this segment could be observed throughout the cardiac cycle. These abnormalities are represented in figure 1.

Four of these animals were studied between 2½ and 3 months after the ventriculotomy. Slight improvement was noted, and right ventricular activity continued to be grossly abnormal.

The six animals undergoing horizontal ventriculotomy showed little change in the contraction pattern of the right ventricle. Functionally these incisions were oriented along the axis of fiber shortening during systole. Ventricular contraction remained vigorous and its sequential character continued undisturbed. There was almost no paradoxical movement even in the immediate vicinity of the incision. The specific activity of the outflow tract was preserved. These observations are illustrated in figure 2.

Figures 3, 4, and 5 illustrate the typical effects of ventriculotomies on right ventricular function curves. After a long vertical ventriculotomy (fig. 3) there is distinct depression. Maximum stroke work is reduced and each increment is performed at rising right atrial pressures. When the vertical ventriculotomy is kept quite short, lesser degrees of impairment are noted (fig. 4). After horizontal ventriculotomy, no significant depression of the curve is noted (fig. 5).

### Discussion

Previous experiences have suggested that right ventricular cardiotomy as customarily performed can be a traumatizing procedure. Moulder and co-workers[13] reported a higher

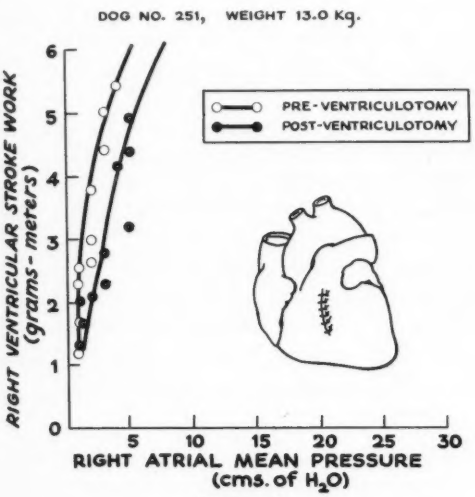


**Figure 4**

*Ventricular function curves before and after a very short vertical right ventriculotomy. The stroke work was calculated over a range of flows, 1.2 to 3.0 L./min./M.². The impairment of function is decidedly less than after a long ventriculotomy.*

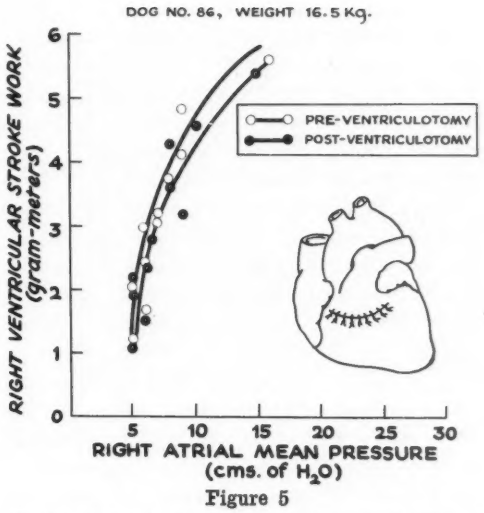


**Figure 5**

*Ventricular function curves before and after a transverse right ventriculotomy. The stroke work was calculated over a range of flows, 1.1 to 3.2 L./min./M.². There is no depression of function.*

incidence of complications after ventriculotomy than after atriotomy or aortotomy. Cooley's group[14] observed that patients tolerate atriotomy better than ventricular incisions and recommended it as the method of choice in the repair of ventricular septal defects that can be palpated through the atrial appendage. Lillehei at one time suggested this approach in patients with pulmonary hypertension.[11] This has also been advocated recently by Kay.[3]

Rams and co-workers[15] made observations in a series of dogs after recovery from right ventriculotomy. They reported ventricular irritability and the precipitation of fatal arrhythmias in one group of animals catheterized postoperatively with the chest closed. A second group was reoperated upon. It was noted that needle puncture of the right ventricle precipitated hazardous arrhythmias. This group had a high mortality and only half survived more than 2 days after reoperation. At autopsy, congestive heart failure was present, the right ventricles were dilated, and hepatomegaly and effusions were present. Stirling and co-workers[11] studied the effects of right ventriculotomy by means of ventricular function curves, noting significant depression when long vertical incisions were made. This was not so apparent when the incisions were kept short or made parallel to the anterior branches of the right coronary artery.

The present data add further support to the foregoing impressions. They contradict previous studies maintaining that extensive damage may be inflicted on the right ventricle without conspicuous functional impairment.[16, 17] Both cinefilm analysis and ventricular function curves indicate that important changes occur in right ventricular contraction and work characteristics after the conventional longitudinal incision. They indicate, too, that transverse incisions are preferable in that they interfere far less with right ventricular physiology. This is consistent with previous knowledge pertaining to the functional anatomy of the right ventricle.[18] The thin external and internal spiral muscles invest the ventricles from base to apex and

combine to shorten the long axis of the chambers. Between these spiral groups, the chambers are enveloped by the deep constrictors, which fan out in horizontally oriented bundles. It is these muscles which in contracting reduce the diameter of the heart. Whereas a vertical ventriculotomy transects the right ventricular constrictor fibers, the horizontal cardiotomy more nearly spits them along their horizontal plane. The latter incision is less likely to damage them functionally just as a muscle-splitting incision anywhere is functionally less disturbing. Moreover, the vertical wound interrupts these bundles throughout its extent from base to apex, while the horizontal one interrupts them at a single level along their axis of shortening, leaving those bundles above and below this site unscathed. Other explanations for the results obtained are not readily forthcoming. Differences in the degree of coronary artery interruption are not obvious, and with both types of incisions, care was taken to spare vessels of appreciable size. Nor does interference with right ventricular conduction appear to play a role, since widening of the QRS complex was noted in only one instance when a vertical ventriculotomy was extended through the base of the anterior papillary muscle.

The clinical implications of this study bear upon the problem of repairing ventricular septal defects with pulmonary hypertension and Fallot's tetralogy. Previous observations have suggested that atriotomy is better tolerated in these conditions than ventriculotomy,[11, 13, 14] and this has been forcefully advocated recently in the treatment of defects associated with pulmonary hypertension.[3] However, atriotomy cannot provide adequate access to the right ventricle on all occasions and ventriculotomy is essential for the proper repair of complicated lesions. It cannot readily be employed, for example, when the ventricular septal defect is anterior nor can it provide inspection of the aortic valve which is in close approximation to these defects. Nor can lesions involving the infundibulum or the pulmonic valve be corrected by this approach.

Transverse ventriculotomy may be a practical alternative. The access it provides is comparable to that of the traditional cardiotomy. As in the latter approach, the precise orientation of the incision has to be tailored to spare the coronary circulation, but in general the distribution of the vessels on the surface of the right ventricle favors the transverse approach. Initial experiences with it in our clinics have been encouraging. There have been no particular difficulties in its application, it is well tolerated, and patients with pulmonary hypertension appear to have a smoother postoperative course.[19]

**Summary**

The effects of right ventricular cardiotomy were investigated in a total of 28 dogs. Half of the group were studied by high-speed cinematography and half by means of ventricular function curves. In both groups long vertical ventriculotomies were done in eight animals and transverse ventriculotomies were performed in six.

Adverse effects on the contraction and function of the right ventricle were observed in the animals undergoing vertical cardiotomy. On the other hand, transverse ventriculotomy did not result in significant abnormalities of right ventricular performance.

It is concluded that transverse ventriculotomy is more physiologic and may be the incision of choice, especially in the higher-risk group of patients with pulmonary hypertension.

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Sometimes, amid campaigns against so many diseases we don't want to die of, I think, somewhat flippantly, that we might sensibly focus our attention on deciding which among several mortal diseases we do like, which exits we prefer; and, in dignified acceptance of the inevitable, we might depart after perhaps less stampeding and general confusion.—Alan Gregg, M.D. *Challenges to Contemporary Medicine.* New York, Columbia University Press, 1956, p. 91.

# Reduction of Serum Cholesterol Concentrations by Neomycin, Para-aminosalicylic Acid, and Other Antibacterial Drugs in Man

*By* PAUL SAMUEL, M.D., AND WILLIAM I. WAITHE, M.S.

IT WAS previously reported that neomycin in daily oral doses of 1.5 to 2 Gm. reduced serum cholesterol levels in man.[1, 2] An extension of these observations, the effect of other antibacterial drugs, and studies on the mechanisms of action are reported here.

## Effect of Antibacterial Drugs on Serum Cholesterol Concentrations

### Material and Methods

Fifty-six patients were studied in 112 experimental periods of 2 to 37 weeks. Twenty-seven patients were male and 29 were female, with an age range of 21 to 76 years. Forty patients were hospitalized and 16 were outpatients. Hospitalized patients were maintained on regular hospital diets in which 40 to 45 per cent of the calories were derived from fat. The food intake of the 16 outpatients was uncontrolled, but they were instructed to adhere to their customary diets. Medications known to influence serum cholesterol concentrations or other antibacterial drugs were not given. Patients were weighed weekly, and blood counts, tests of urine, blood urea nitrogen, serum bilirubin, and cephalin flocculation were carried out periodically.

Serum cholesterol concentrations were determined once a week in the fasting state by the method of Zak et al.[3] after the precipitation of serum with an alcohol-acetone mixture. Serum phospholipid determinations were carried out by the method of Simonsen et al.,[4] and the proportion of cholesterol in the alpha- and beta-lipoproteins was measured by the method of Langan et al.[5] The control serum cholesterol levels, prior to the administration of the drugs, were observed for periods of 6 weeks or longer. When a patient was given different drugs consecutively, an interval of 3 to 12 weeks was interposed, during which cholesterol concentrations returned to control levels, before the next drug was given, except when indicated otherwise. Serum cholesterol concentrations were determined in 48 patients for 3 to 12 weeks after all experimental medications were discontinued.

A preparation containing 70 per cent neomycin base (Mycifradin Sulfate)* was given orally to 30 patients at daily doses of 1.5 to 2 Gm. in two daily doses for periods varying between 4 and 37 weeks. The doses of medication in this study, referred to as neomycin, represent the weight of Mycifradin Sulfate.

The concentrations of esterified cholesterol, phospholipids, and alpha- and beta-cholesterol were determined serially in the serum of 10 subjects during the control period and during oral administration of neomycin. Ten patients were given 60 mg. of neomycin intramuscularly once daily for a period of 3 weeks.

Three patients were given 500 mg. of neamine† (neomycin A) daily for 5 to 6 weeks. The neomycin molecule can be split into two constituents: neamine and neobiosamine. The neamine moiety retains definite antibacterial properties although the range and potency of its activity is somewhat different from that of commercial neomycin.[6]

Para-aminosalicylic acid (PAS) was given to 15 patients in 30 experimental periods for 5 to 23 weeks at daily dose levels varying between 2 and 12 Gm. Six subjects were given 2 Gm. of kanamycin‡ per day orally, for periods of 3 to 8 weeks. Chlortetracycline§ (Aureomycin) was given to 6 patients by mouth in daily doses of 1 to 1.5 Gm. for 3 to 6 weeks. A variety of other antibacterial drugs was administered to small numbers of patients (table 1).

### Results

The results of the oral administration of neomycin are shown in table 2. All 30 cases

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This work was carried out during Dr. Samuel's tenure of a research fellowship from the American Heart Association. His present address is The Long Island Jewish Hospital, New York, New York.

*Supplied by The Upjohn Company, Kalamazoo, Michigan.

†Obtained by courtesy of Dr. Selman A. Waksman and Merck Sharp & Dohme, West Point, Pennsylvania.

‡Supplied by the Bristol Laboratories, Syracuse, New York.

§Supplied by the Lederle Laboratories, Pearl River, New York.

**Table 1**

*Orally Administered Antibacterial Drugs with No Observed Effect on Serum Cholesterol Concentrations*

| Drug | Daily dose | Number of patients | Weeks of medication |
|---|---|---|---|
| Phthalylsulfathiazole* | 6 and 12 Gm. | 2 | 3 and 5 |
| Isoniazid† | 300 mg. | 2 | 4 |
| Penicillin‡ | 1 million units | 2 | 3 |
| Dihydrostreptomycin§ | 2 to 3 Gm. | 3 | 2 to 3 |
| Oxytetracycline§ | 1 Gm. | 2 | 3 |
| Chloramphenicol‖ | 1 Gm. | 2 | 3 |
| Polymyxin§ | 150 mg. | 2 | 2 and 3 |
| Erythromycin‡ | 1 Gm. | 2 | 3 and 4 |
| Novobiocin* | 1 Gm. | 2 | 3 and 4 |
| Carbomycin§ | 1 Gm. | 2 | 3 |
| Bacitracin§ | 20,000 units | 2 | 2 |
| Viomycin§ | 2 to 3 Gm. | 4 | 3 |

*Supplied by the Merck Sharp and Dohme Laboratories.
†Supplied by Eli Lilly and Co.
‡Supplied by Abbott Laboratories.
§Supplied by Pfizer Laboratories.
‖Supplied by Parke, Davis and Co.

showed a fall in serum cholesterol, the mean decrease being 21 per cent. Serum cholesterol level reached a low point after 1 to 3 weeks of neomycin administration and remained there as long as neomycin was administered, returning to control levels 1 to 8 weeks later (figs. 1, 2, and 3).

More complete studies of the serum lipids were made in 10 patients, eight of whom had clinical vascular disease or diabetes mellitus. The concentration of esterified cholesterol and of phospholipids decreased in the serum in proportion to the fall of total cholesterol. The average of the esterified fraction of cholesterol of the 10 patients was 78 per cent of the total during the control period and 77 per cent during the administration of neomycin. The average cholesterol-phospholipid ratio was 1.2, both before and during neomycin administration. The average concentration of beta-lipoprotein cholesterol in the serum was 83 per cent of the total cholesterol during the control period and 82 per cent after the reduction of serum cholesterol by neomycin.

Oral administration of neomycin was combined with other antibacterial drugs in seven instances. The second drug was added after the concentration of serum cholesterol was reduced by neomycin to its low point. Two grams of mandelamine for 2 weeks, 15 Gm. of phthalylsulfathiazole for 5 weeks, 300 mg. of isoniazid for 7 weeks, and 1 Gm. of oxytetracycline for 3 weeks were added daily to the neomycin regimen without influencing the effect of neomycin (fig. 3).

The results of daily intramuscular administration of 60 mg. of neomycin are summarized in table 3. In the 10 patients studied, the daily intramuscular injection of the drug failed to alter the concentration of serum cholesterol (figs. 1 and 3).

No major side effects occurred during the administration of neomycin. Ten of the 30 patients who were given neomycin orally developed temporary, mild diarrhea that was usually controlled easily with tincture of paregoric; in one case neomycin had to be discontinued at the end of 6 weeks. The weight of the patients did not vary more than 2 lbs. in a period of 6 months. The hematopoietic, hepatic, and renal functions were not altered.

Neamine, given by mouth, also reduced serum cholesterol in three patients (table 4 and fig. 2).

The results of PAS administration at different dose levels are shown in table 5. Eleven of the 15 subjects had pulmonary tuberculosis. These patients were given 300 mg. of isoniazid

**Table 2**

*Effect of Oral Administration of Neomycin on Average Total Serum Cholesterol Level (mg./100 ml.) in Thirty Patients*

| Patient, age, sex | Diagnosis | Weeks on medicaton | Daily dose Gm. | Average total cholesterol | | | |
|---|---|---|---|---|---|---|---|
| | | | | Control | Neomycin | Per cent fall | $p<$ |
| J.F. 42 M | Cerebrovascular accident | 37 | 2 | 268 ± 24* | 219 ± 12* | 18 | 0.001 |
| N.K. 62 M | Coronary artery disease | 26 | 2 | 383 ± 17 | 309 ± 21 | 19 | 0.001 |
| P.W. 58 F | Cerebrovascular accident | 20 | 2 | 355 ± 18 | 273 ± 34 | 23 | 0.001 |
| A.W. 53 M | Cerebrovascular accident | 20 | 2 | 229 ± 18 | 176 ± 12 | 23 | 0.001 |
| J.G. 44 M | Paraplegia of undetermined cause | 19 | 2 | 264 ± 14 | 210 ± 15 | 20 | 0.001 |
| C.U. 36 F | Familial hypercholesteremia | 16 | 2 | 379 ± 14 | 286 ± 23 | 24 | 0.001 |
| A.M. 55 M | Cerebrovascular accident | 15 | 2 | 314 ± 17 | 238 ± 26 | 24 | 0.001 |
| J.H. 42 M | Coronary artery disease | 13 | 1.5 | 342 ± 18 | 284 ± 23 | 17 | 0.001 |
| J.R. 68 M | Coronary artery disease | 12 | 1.5 | 274 ± 19 | 227 ± 16 | 17 | 0.001 |
| W.C. 47 M | Coronary artery disease | 12 | 1.5 | 256 ± 17 | 211 ± 6 | 17 | 0.001 |
| B.C. 57 F | Coronary artery disease, cerebrovascular accident, diabetes mellitus | 12 | 2 | 292 ± 17 | 232 ± 28 | 20 | 0.001 |
| M.S. 73 F | Peripheral vascular disease | 11 | 2 | 210 ± 15 | 166 ± 9 | 21 | 0.001 |
| R.R. 52 F | Diabetes mellitus | 10 | 2 | 339 ± 26 | 269 ± 19 | 20 | 0.001 |
| T.D. 58 M | Tabes dorsalis | 10 | 2 | 235 ± 18 | 194 ± 17 | 17 | 0.001 |
| R.M. 54 M | Pulmonary tuberculosis | 10 | 2 | 244 ± 12 | 197 ± 11 | 19 | 0.001 |
| A.Z. 48 F | Familial hypercholesteremia | 9 | 1.5 | 513 ± 37 | 378 ± 59 | 26 | 0.001 |
| J.B. 68 M | Coronary artery disease | 8 | 1.5 | 293 ± 5 | 232 ± 7 | 21 | 0.001 |
| M.L. 44 F | Cerebrovascular accident | 7 | 2 | 292 ± 13 | 238 ± 10 | 18 | 0.001 |
| R.O. 46 F | Cerebrovascular accident, diabetes mellitus | 7 | 2 | 304 ± 27 | 251 ± 22 | 17 | 0.005 |
| D.F. 55 M | No clinical disease | 7 | 2 | 260 ± 16 | 224 ± 11 | 14 | 0.001 |
| A.T. 59 F | Familial hypercholesteremia | 6 | 1.5 | 438 ± 21 | 321 ± 28 | 28 | 0.001 |
| J.D. 21 F | Paraplegia of undetermined cause | 6 | 2 | 194 ± 12 | 158 ± 12 | 19 | 0.001 |
| A.B. 61 M | Coronary artery disease, familial hyperlipemia | 5 | 2 | 305 ± 17 | 249 ± 7 | 18 | 0.001 |
| G.L. 60 F | Cerebrovascular accident | 5 | 2 | 394 ± 48 | 281 ± 27 | 29 | 0.001 |
| J.M. 35 M | Multiple sclerosis | 5 | 2 | 158 ± 11 | 125 ± 19 | 21 | 0.005 |
| V.N. 41 F | Multiple sclerosis | 5 | 2 | 190 ± 11 | 142 ± 10 | 25 | 0.001 |
| M.L. 56 F | Cerebrovascular accident | 5 | 2 | 321 ± 23 | 241 ± 19 | 25 | 0.001 |
| T.S. 51 M | Pulmonary tuberculosis | 5 | 2 | 322 ± 16 | 230 ± 9 | 28 | 0.001 |
| H.Z. 63 M | Coronary artery disease | 4 | 1.5 | 273 ± 18 | 203 ± 7 | 27 | 0.001 |
| D.L. 58 F | No clinical disease | 4 | 2 | 313 ± 22 | 254 ± 18 | 19 | 0.005 |

*Standard deviation.

daily and 1 Gm. of streptomycin intramuscularly twice weekly, in addition to the experimental PAS medication. The administration of isoniazid and streptomycin was maintained during the entire study, including the control periods, and was ultimately demonstrated not to influence serum cholesterol concentrations. At lower dose levels of 2 to 6 Gm., PAS reduced cholesterol levels in one half of 14 experiments; at doses of 8 to 12 Gm., serum cholesterol fell in each of 16 experiments. The concentration of serum cholesterol was lowered 1 to 4 weeks after PAS was started and remained low as long as the drug was given, returning to control levels 1 to 3 weeks after discontinuance of PAS (fig. 4).

In two patients cholesterol levels were measured during the administration of PAS, neomycin and PAS, and neomycin alone (fig. 5). There was no significant difference during these three study periods.

Mild nausea was noted periodically, pri-

**Table 3**

*Effect of Intramuscular Administration of Neomycin (60 mg. Daily) for Three Weeks on Average Total Serum Cholesterol Level (mg./100 ml.) in Ten Patients*

| Patient, age, sex | | | Diagnosis | Average total cholesterol | | |
|---|---|---|---|---|---|---|
| | | | | Control | Neomycin | $p >$ |
| F.G. | 43 | M | Cerebrovascular accident | 242 ± 26* | 260 ± 14* | 0.2 |
| J.M. | 35 | M | Multiple sclerosis | 158 ± 11 | 168 ± 0 | 0.025 |
| M.L. | 56 | F | Cerebrovascular accident | 321 ± 23 | 303 ± 21 | 0.2 |
| R.R. | 52 | F | Diabetes mellitus | 339 ± 26 | 322 ± 19 | 0.1 |
| R.O. | 46 | F | Cerebrovascular accident, diabetes mellitus | 304 ± 27 | 306 ± 25 | 0.5 |
| J.G. | 44 | M | Paraplegia of undetermined cause | 264 ± 14 | 269 ± 20 | 0.5 |
| T.D. | 58 | M | Tabes dorsalis | 235 ± 18 | 237 ± 6 | 0.5 |
| M.S. | 73 | F | Peripheral vascular disease | 210 ± 15 | 207 ± 7 | 0.5 |
| A.S. | 65 | F | Paraplegia of undetermined cause | 242 ± 13 | 249 ± 28 | 0.5 |
| J.D. | 21 | F | Paraplegia of undetermined cause | 194 ± 12 | 196 ± 0 | 0.5 |

*Standard deviation.

marily during the use of higher doses of PAS, but no patient's weight varied more than 2 lbs. during the study. A mild diarrhea, similar in character to that following the use of neomycin occurred in four of 15 patients. This, however, did not influence the reduction of serum cholesterol, and was rapidly controlled. No other side effects were observed.

Kanamycin reduced serum cholesterol levels in three of six patients (table 4). The daily administration of 1 to 1.5 Gm. of chlortetracycline (table 4) resulted in a reduction of average serum cholesterol in four of six patients. An easily controlled diarrhea of the previously described type occurred in one patient (D.F.) during the administration of kanamycin, and another in the chlortetracycline group (R.J.), without affecting the lowering of serum cholesterol. A variety of other antibacterial drugs, administered to a small number of patients (table 1), failed to alter serum cholesterol concentrations.

## Serum Concentrations of Neomycin after Oral and Intramuscular Administration

### Material and Methods

Ten hospitalized patients were studied, five of them from the previous experimental group. None of the patients had evidence of kidney or liver disease. No other antibacterial drugs were given prior to or during the experiment. One gram of neomycin was administered orally, twice daily at 8-hour intervals, to three patients. A single dose of 2 Gm. of neomycin was given to five subjects. In three of these patients the 24-hour urinary output of neomycin was measured. Finally, five patients were given a single injection of 60 mg. of neomycin intramuscularly. Urine was collected from each subject, and the 24-hour excretion of neomycin was measured. Serum specimens were obtained before and serially during 12 to 24 hours after administration of the drug.

Serum and urinary concentrations of neomycin were determined by the cylinder-plate method of Grove and Randall,[7] with *Staphylococcus aureus* ATCC 6538 as a test organism. Specimens were tested undiluted. Standard curves of neomycin, diluted in phosphate buffer pH 8, were established with antibiotic-free, aseptically collected, normal human serum and urine.

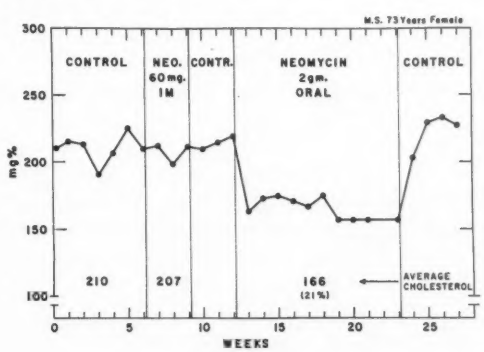


**Figure 1**

*Effect of intramuscular and oral administration of neomycin on serum cholesterol concentrations.*

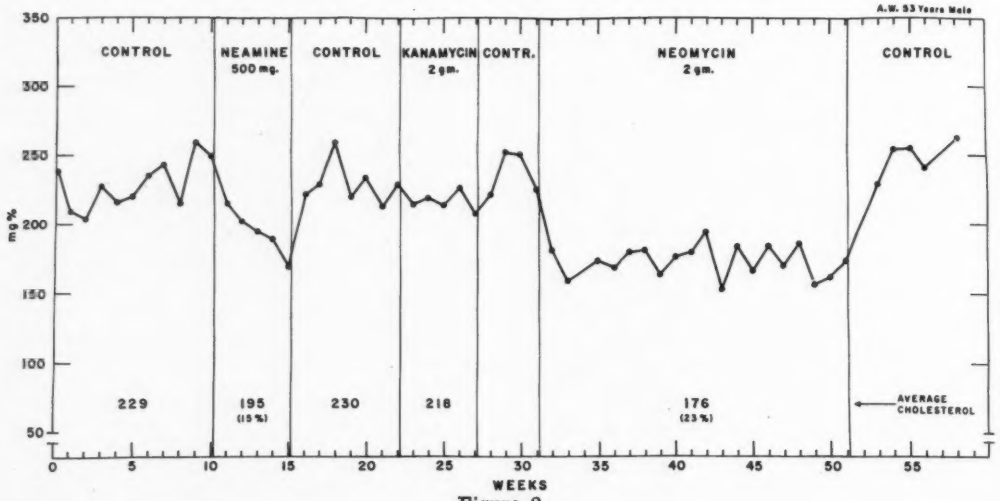


**Figure 2**

*Effect of oral administration of neamine, kanamycin, and neomycin on serum cholesterol concentrations.*

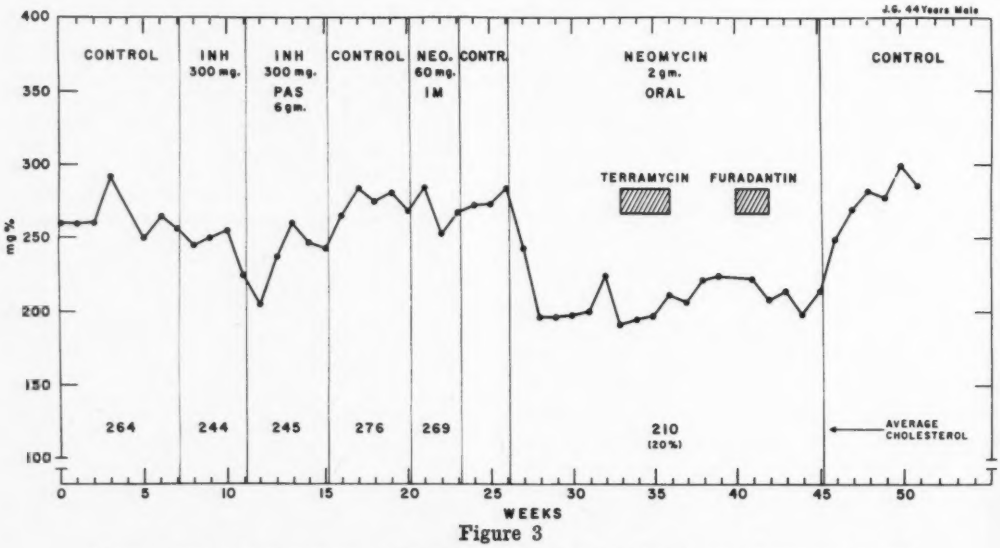


**Figure 3**

*Effect of oral administration of isoniazid (INH), PAS (6 Gm.), and intramuscular and oral neomycin on serum cholesterol concentrations. Oxytetracycline (Terramycin) and furadantin were subsequently added to the oral administration of neomycin.*

**Results**

In the three patients who received 1 Gm. of neomycin orally twice in 8-hour intervals, only traces of the drug could be found in the serum (table 6). When a single dose of 2 Gm. of neomycin was given orally, the average serum concentration of the drug reached its peak value after 2 hours (table 7A) of 0.28 μg. per milliliter. When a single intramuscular dose of 60 mg. of neomycin was injected, the average peak concentration (3.4 μg. per milliliter) in the serum was reached after 1

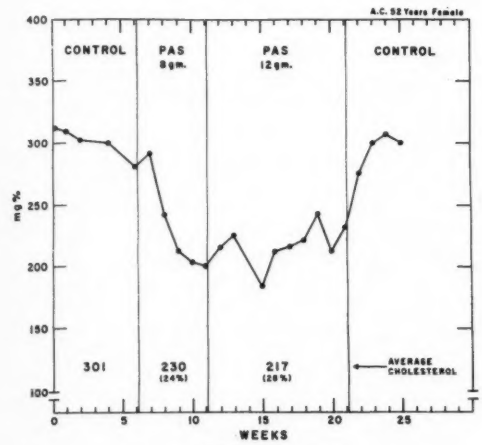


**Figure 4**

*Effect of oral administration of 8 and 12 Gm. of PAS on serum cholesterol concentrations.*

hour (table 7B). This medication did not alter serum cholesterol levels (table 3), although the average serum concentrations of the drug were 12-fold higher after the injection of 60 mg. than after an oral dose of 2 Gm.

### Concentration of Neomycin in the Bile after Oral and Intramuscular Administration

#### Material and Methods

Four hospitalized patients (table 8) were studied who underwent cholecystectomy because of cholelithiasis and cholecystitis. A T-tube was placed in the common hepatic duct by the surgeon, through which drained 250 to 600 ml. of bile daily prior to and during the experiment. The tests were performed 4 to 17 days after the operation. The patients were afebrile, out of bed, had normal kidney function, were orally fed, and were not given other antibacterial drugs for 6 days or longer at the time of the experiment. A single oral dose of 2 Gm. of neomycin was given to four patients. Subsequently, (in 2- to 4-day intervals) a single intramuscular injection of 60 mg. was administered to three of these subjects. Serum, bile, and urine specimens were collected before and serially during the 24 hours that followed administration of the drug.

Serum and urinary concentrations of neomycin were determined as described. Urine was diluted with phosphate buffer pH 8, whenever necessary. Studies on the bile blanks and standard curves for neomycin were established by diluting neomycin with antibiotic-free bile, aseptically collected individually from each patient prior to the tests in

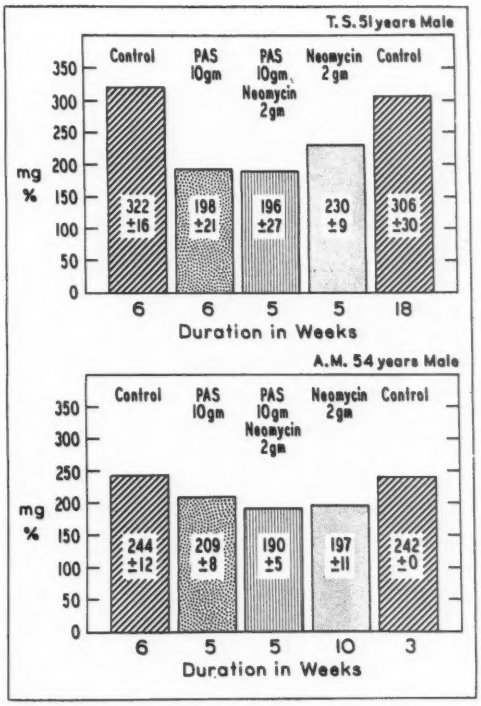


**Figure 5**

*Effect of oral administration of PAS, combined administration of PAS and neomycin, and neomycin alone on serum cholesterol concentrations. (Average serum cholesterol levels and standard deviations.)*

each of the four subjects, by the technical procedure described above.[7] Each individual's bile was also used for the standard reference points in his assay.

#### Results

The concentration of neomycin in the bile, serum, and urine, following the oral administration of 2 Gm. and the intramuscular injection of 60 mg. of the drug, are shown in table 8. Following the oral administration of neomycin, small amounts appeared in the serum and were found erratically in the bile. Significant amounts, however, appeared in the urine. Following the intramuscular injection of neomycin, appreciable serum levels were maintained in the blood for at least 8 hours. During this time its presence in the bile could be demonstrated, and its concentration in the

**Table 4**

*Effect of Oral Administration of Neamine, Kanamycin, and Chlortetracycline (Aureomycin) on Average Total Serum Cholesterol Concentrations*

| Patient, age, sex | | Diagnosis | Drug and daily dose | Weeks on medication | Average total cholesterol | | | $p$ |
|---|---|---|---|---|---|---|---|---|
| | | | | | Control | Medication | Per cent fall | |
| M.L. | 44 F | Cerebrovascular accident | Neamine, 500 mg. | 6 | 292 ± 13* | 245 ± 9* | 16 | <0.001 |
| C.B. | 43 F | Cerebrovascular accident, diabetes mellitus | Neamine, 500 mg. | 6 | 256 ± 12 | 236 ± 16 | 8 | <0.025 |
| A.W. | 53 M | Cerebrovascular accident | Neamine, 500 mg. | 5 | 229 ± 12 | 195 ± 19 | 19 | <0.001 |
| L.D. | 44 M | Peripheral vascular disease | Kanamycin, 2 Gm. | 8 | 230 ± 16 | 200 ± 7 | 15 | <0.005 |
| Z.A. | 47 F | Familial hypercholesteremia | Kanamycin, 2 Gm. | 7 | 545 ± 25 | 499 ± 16 | 8 | <0.005 |
| B.A. | 62 M | Coronary artery disease | Kanamycin, 2 Gm. | 5 | 357 ± 10 | 321 ± 25 | 10 | <0.025 |
| A.W. | 53 M | Cerebrovascular accident | Kanamycin, 2 Gm. | 5 | 229 ± 18 | 218 ± 7 | — | >0.1 |
| D.F. | 55 M | No clinical disease | Kanamycin, 2 Gm. | 5 | 260 ± 16 | 250 ± 25 | — | >0.4 |
| L.I. | 50 M | Cerebrovascular accident | Kanamycin, 2 Gm. | 3 | 224 ± 16 | 222 ± 16 | — | >0.5 |
| B.A. | 62 M | Coronary artery disease | Chlortetracycline, 1.5 Gm. | 6 | 357 ± 10 | 289 ± 29 | 19 | <0.001 |
| N.K. | 62 M | Coronary artery disease | Chlortetracycline, 1.5 Gm. | 5 | 383 ± 17 | 355 ± 36 | 7 | >0.1 |
| M.J. | 34 M | Spinal cord injury | Chlortetracycline, 1 Gm. | 5 | 204 ± 12 | 183 ± 10 | 10 | <0.01 |
| M.L. | 44 F | Cerebrovascular accident | Chlortetracycline, 1 Gm. | 4 | 292 ± 13 | 251 ± 10 | 14 | <0.001 |
| R.J. | 66 M | Coronary artery disease | Chlortetracycline, 1 Gm. | 4 | 321 ± 18 | 291 ± 13 | 9 | <0.01 |
| Z.A. | 47 F | Familial hypercholesteremia | Chlortetracycline, 1 Gm. | 3 | 545 ± 25 | 545 ± 46 | — | >0.5 |

*Standard deviation.

urine remained constant at a level of about 50 $\mu$g. per milliliter.

### Radioactive Fat Absorption Studies

#### Material and Methods

Four patients were studied, all of whom were included in the study group on the effect of neomycin. Three were hospitalized, and one was an outpatient. Two radioactive fat-absorption tests were carried out in each patient. At the time of the initial test the patients had been maintained on oral neomycin (2 Gm. daily) for 9, 10, 12, and 18 weeks, respectively. The second test was performed after the administration of neomycin was discontinued for 4, 5, 5, and 7 weeks respectively, by which time serum cholesterol concentrations had returned to control levels in each patient.

The patients were given 10 drops of Lugol's solution USP on the day preceding the test, and once each day thereafter for 72 hours. After an overnight fast, a test breakfast consisting of 50 ml. of olive oil, 50 ml. of milk, 200 Gm. of ice cream (melted together) and 2 slices of bread was given, accompanied by a capsule of 50 $\mu$c. of $I^{131}$-labeled triolein. Scheduled medications, if any, were given together with the meal, and regular feeding was resumed at lunch time. Blood was collected in oxalated tubes serially during the 24 hours that followed the test meal, and stools were collected at 24-hour periods in separate containers for 72 hours after the beginning of the experiment. Total blood radioactivity was read against the standard in 4-ml. aliquots, and the per cent absorption was calculated from standard blood-volume charts according to sex, weight, and height. Total fecal radioactivity was measured separately on each 24-hour stool specimen.

In normal subjects under the present experimental conditions the radioactivity of serum reached 10 per cent or more of the ingested amount by the sixth hour of the experiment, and then declined progressively. The total radioactivity of the stools normally did not exceed 5 per cent of the amount given during the 72 hours following the test.

#### Results

On the day of the initial test, serum cholesterol concentrations had been lowered to 157, 163, 195, and 257 mg. per cent respectively, by long-term administration of oral neomycin, in the four patients studied. When the second tests were carried out the respective serum cholesterol levels of these patients were 229, 264, 243, and 371 mg. per cent. In three of the four patients (fig. 6A, B, and D)

**Table 5**

*Effect of Oral Administration of PAS on Average Total Serum Cholesterol Level (Mg./100 Ml.) in Thirty Patients*

| Patient, age, sex | Diagnosis | Control, cholesterol* | Dose of PAS (Gm.) | Weeks† | Cholesterol during PAS* | Per cent fall | p |
|---|---|---|---|---|---|---|---|
| R.B. 32 F | Pulmonary tuberculosis | 295 ± 24 | 8 | 5 | 216 ± 18 | 27 | <0.001 |
| | | | 10 | 6 | 196 ± 19 | 34 | <0.001 |
| | | | 12 | 6 | 230 ± 13 | 22 | <0.001 |
| R.M. 54 M | Pulmonary tuberculosis | 244 ± 12 | 8 | 7 | 202 ± 16 | 17 | <0.001 |
| | | | 10 | 5 | 209 ± 8 | 14 | <0.001 |
| | | | 12 | 7 | 183 ± 20 | 25 | <0.001 |
| B.J. 52 F | Pulmonary tuberculosis | 314 ± 28 | 6 | 7 | 260 ± 18 | 17 | <0.005 |
| | | | 10 | 7 | 264 ± 26 | 16 | <0.01 |
| | | | 12 | 6 | 221 ± 21 | 29 | <0.001 |
| T.S. 51 M | Pulmonary tuberculosis | 322 ± 16 | 4 | 11 | 256 ± 15 | 20 | <0.001 |
| | | | 8 | 6 | 217 ± 34 | 32 | <0.001 |
| | | | 10 | 6 | 198 ± 21 | 38 | <0.001 |
| M.N. 23 F | Pulmonary tuberculosis | 194 ± 12 | 2 | 5 | 203 ± 14 | — | >0.2 |
| | | | 4 | 5 | 192 ± 18 | — | >0.5 |
| | | | 6 | 5 | 159 ± 12 | 18 | <0.001 |
| A.B. 61 M | Coronary artery disease | 305 ± 17 | 6 | 4 | 299 ± 22 | — | >0.5 |
| | Familial hyperlipemia | | 12 | 4 | 226 ± 12 | 26 | <0.001 |
| A.C. 52 F | Pulmonary tuberculosis | 301 ± 12 | 8 | 5 | 230 ± 38 | 24 | <0.001 |
| | | | 12 | 10 | 217 ± 19 | 28 | <0.001 |
| M.M. 43 F | Rheumatic heart disease | 244 ± 18 | 6 | 4 | 235 ± 12 | — | >0.1 |
| | | | 12 | 9 | 185 ± 31 | 24 | <0.001 |
| S.L. 67 M | Pulmonary tuberculosis | 169 ± 17 | 4 | 6 | 107 ± 12 | 36 | <0.001 |
| | | | 6 | 9 | 127 ± 20 | 24 | <0.005 |
| M.B. 53 F | Pulmonary tuberculosis | 323 ± 18 | 2 | 5 | 309 ± 42 | — | >0.5 |
| | | | 4 | 7 | 287 ± 17 | 11 | <0.01 |
| E.M. 31 F | Pulmonary tuberculosis | 318 ± 24 | 12 | 6 | 178 ± 25 | 44 | <0.001 |
| J.G. 44 M | Paraplegic of undetermined cause | 264 ± 14 | 6 | 5 | 245 ± 26 | — | >0.1 |
| C.W. 30 F | Pulmonary tuberculosis | 222 ± 10 | 6 | 6 | 149 ± 8 | 32 | <0.001 |
| J.W. 55 F | Pulmonary tuberculosis | 239 ± 17 | 10 | 5 | 191 ± 10 | 20 | <0.001 |
| F.J. 43 M | Cerebrovascular accident | 242 ± 26 | 6 | 5 | 230 ± 26 | — | >0.4 |

*Average and standard deviation.

†Weeks on para-aminosalicylic acid (PAS).

the shape of the absorption curve was the same during neomycin and control periods. Total stool radioactivity ranged from 0 to 2.4 per cent, with no significant difference between the neomycin and control periods. One patient (fig. 6C) showed a somewhat higher absorption during the control period, but even in this case the absence of radioactivity in the stools indicated a complete but late absorption. The persistence of a flat absorption curve, despite the rise in serum cholesterol in the fourth patient (fig. 6D), may indicate that delayed absorption was independent of the presence of neomycin. If it was a consequence of the administration of the drug, the lowering of the serum cholesterol level was not related to delayed fat absorption.

## Discussion

Neomycin is widely used orally to disinfect the intestinal tract. The rapid decrease of the total bacterial count in the feces during the first few days of administration is followed by overgrowth of nonsusceptible microorganisms.[6] Although the short-term changes of the intestinal flora have been repeatedly described, only scanty data are available following its long-term use. The long-term oral

**Table 6**

*Serum Concentrations of Neomycin (μg./ml.) Following the Oral Administration of Two Successive Doses of 1 Gm.*

| Patient, age, sex | | | Hours | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | 0* | 1 | 2 | 3 | 4 | 8* | 9 | 10 | 11 | 12 |
| T.D. | 58 | M† | 0 | 0 | 0 | 0 | Tr‡ | Tr | Tr | Tr | 0 | 0 |
| J.F. | 42 | M | 0 | 0 | Tr | Tr | Tr | Tr | Tr | Tr | Tr | Tr |
| C.D. | 62 | M | 0 | 0 | Tr | Tr | 0 | 0 | 0 | Tr | Tr | Tr |

*Neomycin, 1 Gm., was given at zero hour and also at the eighth hour.

†Two grams of oral neomycin daily for 6 weeks prior to test.

‡Traces (less than 0.2 μg./ml.).

administration of the drug alters significantly the character of the intestinal bacterial flora.[6]

It is generally accepted that neomycin is poorly absorbed from the gastrointestinal tract,[8] whereas rapid diffusion and distribution of the drug are observed after its parenteral administration. In the present study the intramuscular administration of 60 mg. of neomycin resulted in 12-fold higher average serum concentrations than oral doses of 2 Gm. Since oral neomycin lowered serum cholesterol concentrations significantly, whereas the above intramuscular doses failed to alter the level of serum cholesterol, it is suggested that the effect of the drug is dependent upon its activity in the gastrointestinal tract. Furthermore, the experiments on the biliary excretion of neomycin suggest that the biliary excretion of the drug is probably derived from the general circulation, and that the existence of an enterohepatic circulation of the drug, and thus its direct action upon the liver cell when administered orally, is unlikely.

In contrast to data on man neomycin appears to be ineffective in lowering the serum cholesterol level in normal and cholesterol-fed rats,[9] and in cholesterol-fed rabbits.[10] In fact, in rats fed cholesterol and cholic acid, neomycin appeared to increase serum cholesterol concentrations and aortic sudanophilia.[11]

In the present study, the oral use of neomycin seemed to be well tolerated over long periods of time in patients without kidney impairment. The only side effect was a temporary mild diarrhea in about one third of the subjects treated orally. Any relation of the cholesterol-lowering activity of the drug to diarrhea is highly unlikely, since the duration of diarrhea was insignificant compared to the length of the experiments, and patients without diarrhea exhibited similar reduction in serum cholesterol. Furthermore, the administration of other antibiotics, which failed to lower serum cholesterol levels, caused diarrhea as frequently as neomycin. Finally no patient lost more than 2 lbs. of weight in the group treated with neomycin. Stormont et al.[12] reported severe diarrhea in three of 68 cirrhotic patients treated for hepatic coma with oral doses of 4 to 8 Gm. of neomycin daily. Monilia was cultured in the stools of two of these three cases. Last and Sherlock[13] reported the case of a patient with cirrhosis and hepatic coma, treated by oral daily doses of initially 12 then 4 Gm. of neomycin for over 140 days, followed by deafness, which was ascribed to the toxicity of the drug.

Faloon, Jacobson, and associates,[14, 15] described an "experimental malabsorption syndrome" associated with steatorrhea and morphologic changes of jejunal mucosa[16] following daily oral doses of 12 Gm. of neomycin. This syndrome had to be considered in searching for the mechanism of the cholesterol-lowering action of the drug, although in the present study serum cholesterol concentrations were reduced with considerably lower doses of neomycin. Radioactive fat-absorption tests, in the present study, have indicated that the long-term oral administration of 2 Gm. of neomycin per day, accompanied by significant reduction of serum cholesterol concentrations, resulted in no alteration in the normal fat-absorption patterns in two subjects, and in a delayed but complete absorp-

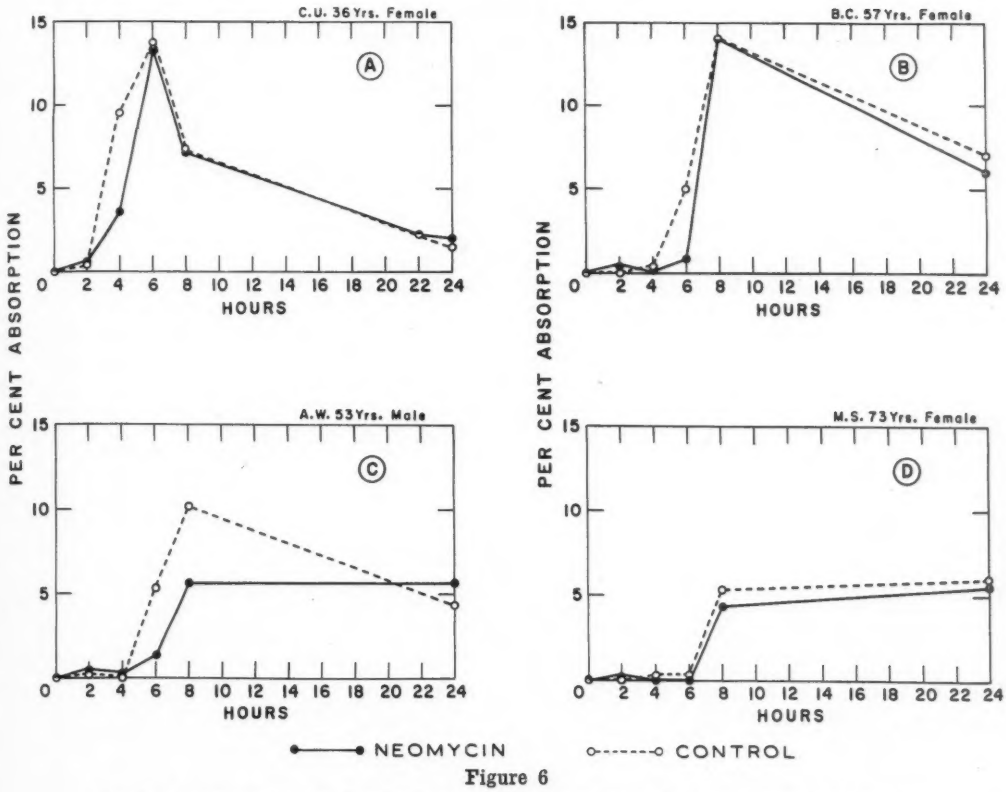


**Figure 6**

*Results of radioactive fat-absorption tests in four patients after long-term administration of neomycin and during control periods.*

tion of fats in two other patients. These data suggest that the cholesterol-reducing activity of neomycin is not dependent for its effect on absorption of dietary fats.

Among the diverse antibacterial drugs used in this study, the antibacterial activity and molecular structure of neamine and kanamycin resemble that of neomycin.[6, 17] The mechanism of their moderate cholesterol-lowering effect is possibly similar to that of neomycin. The oral use of PAS may cause irritation of the gastrointestinal mucosa and was reported to result in hepatic toxicity.[18] Tygstrup et al. published a preliminary report[19] on the cholesterol-lowering effect of PAS, comparable to the results of this study. Chlortetracycline was reported to cause liver toxicity in patients,[20] and Nelson et al.[21] reported that the addition of chlortetracycline to the regimen of cholesterol-fed rabbits augmented the serum cholesterol concentrations and vascular atheromatosis of the animals.

There is no evidence available to explain the serum cholesterol-lowering effect of these diverse antibacterial drugs. Although PAS and chlortetracycline are readily absorbed, one cannot rule out the possibility that their action would be mediated through changes in the gastrointestinal tract. There is no close chemical resemblance between the molecular structures of PAS or chlortetracycline and that of neomycin. The only common denominator between these substances is their antibacterial activity. It should be pointed out that, although a variety of other antibacterial drugs failed to lower serum cholesterol con-

**Table 7A**

*Serum Concentrations of Neomycin (μg./ml.) Following the Administration of a Single Oral Dose of 2 Gm.*

| Patient age, sex | Weeks* | Hours 0 | 1 | 2 | 3 | 4 | 8 | 24 | 24-Hour urinary output (mg.) |
|---|---|---|---|---|---|---|---|---|---|
| A.W. 53 M | 20 | 0 | 0.6 | 0.3 | 0.2 | Tr† | Tr | 0 | 7.0 |
| B.C. 57 F | 11 | — | 0 | Tr | Tr | Tr | 0 | 0 | 9.6 |
| R.M. 54 M | 8 | 0 | Tr | 0.5 | 0 | Tr | 0 | 0 | 8.7 |
| J.F. 42 M | — | 0 | 0.4 | 0.2 | Tr | Tr | 0 | 0 | — |
| J.P. 51 M | — | — | Tr | 0.3 | Tr | Tr | 0 | 0 | — |
| Average | | 0 | 0.24 | 0.28 | Tr | Tr | 0 | 0 | 8.4 |

*Weeks on neomycin at time of test.

†Traces (less than 0.2 μg./ml.).

**Table 7B**

*Serum Concentrations of Neomycin (μg./ml.) Following the Administration of a Single Intramuscular Dose of 60 mg.*

| Patient age, sex | Weeks* | Hours ½ | 1 | 2 | 3 | 4 | 8 | 24 | 24-Hour urinary output (mg.) |
|---|---|---|---|---|---|---|---|---|---|
| M.B. 58 F | 3 | 2.1 | 4.3 | 3.3 | 1.7 | 1.6 | 0.5 | 0 | 30 |
| C.D. 62 M | 3 | — | 4.1 | 3.2 | 1.6 | 1.1 | 0.6 | 0 | 21 |
| J.F. 42 M | 3 | 3.2 | 2.8 | 2.0 | 1.5 | 0.9 | 0 | 0 | 28 |
| G.F. 48 M | — | 1.5 | 1.8 | 1.3 | 0.7 | 0.5 | Tr | 0 | 19.2 |
| J.P. 51 M | — | 3.0 | 4.0 | 2.0 | 1.1 | 1.1 | 0.2 | 0 | 14.5 |
| Average | | 2.5 | 3.4 | 2.4 | 1.3 | 1.0 | 0.3 | 0 | 22.5 |

*Weeks on neomycin at time of test.

centrations in this study, these drugs were each used only in a relatively small number of patients for comparatively short periods.

At present, the exact mechanism of the cholesterol-lowering action of neomycin is not understood. The effect of the drug may be due to modifications of the character of the intestinal bacterial flora or inhibition of intestinal enzyme systems involved in the specific absorption of cholesterol.

The possible role of intestinal bacteria in cholesterol metabolism was mentioned as early as 1896.[22] More recently Rosenheim and Webster[23] found that the administration of succinyl sulfathiazole to cholesterol-fed rats inhibited completely the formation of coprosterol. This was accompanied by a decrease of the number of *Escherichia coli* in the intestine of the animals. Curran and Brewster[24] obtained from the duodenum of patients with chronic cholecystitis a strain of *Esch. coli,* capable of liberating carbon dioxide from labeled cholesterol "in vitro." Wainfan et al.[25] demonstrated that the administration of succinyl sulfathiazole and streptomycin to cholesterol-fed mice inhibited the destruction of cholesterol in the carcass of the animals, concomitant with a striking decrease in the number of intestinal bacteria. In a later series of experiments[26] the same authors isolated 15 bacterial species from the feces and intestinal contents of cholesterol-fed rats, which destroyed or modified cholesterol "in vitro." The addition of dinitrophenol, nicotinamide, or thyroxine and related compounds[27] to the media increased significantly the activity of the bacteria upon cholesterol. Abell, Mosbach, and Kendall[28] suggested that the action of thiouracil on the cholesterol and bile acid metabolism of the dog might be related to the effect of this substance upon the intestinal bacterial flora. Ahrens[29] has also emphasized the possible importance of intestinal bacteria in the metabolism of cholesterol.

Danielsson and Gustafsson[30] reported that germ-free rats had significantly higher serum cholesterol values than controls, and that cholesterol was not reduced to coprostanol in the

**Table 8**

*Concentration of Neomycin (μg./ml.) in the Serum, Bile, and Urine of Patients with Postcholecystectomy Biliary Drainage, after a Single Oral and Intramuscular Dose of the Drug*

| Patient age, sex | | Neomycin, 2 Gm. orally Hours | | | | | | | Neomycin, 60 mg. intramuscularly Hours | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | 0 | 1 | 2 | 4 | 6 | 8 | 24 | 0 | 1 | 2 | 4 | 6 | 8 | 24 |
| M.M. 75 M* | Serum | 0 | 0 | Tr† | Tr | Tr | 0 | — | 0 | 2.0 | 2.8 | 2.0 | 1.5 | 1.3 | 0 |
| | Bile | 0 | 0 | 0 | 0 | 0 | Tr | 0 | 0 | 0 | 0.5 | 0.3 | 0.5 | Tr | 0 |
| | Urine | 0 | 17.5 | — | 10.8 | 12.3 | 14.5 | 0 | — | — | 49.2 | 46.6 | 57.0 | 60.0 | — |
| H.F. 55 F | Serum | 0 | 0 | 0.6 | 0.3 | 0.3 | 0.3 | 0 | 0 | 1.6 | — | 1.1 | 1.4 | 0.5 | — |
| | Bile | 0 | 0 | 0 | 0 | 0 | 1.5 | 0 | 0 | 1.8 | 1.1 | 0.7 | 0 | 0 | 0 |
| | Urine | 0 | 0 | 9.5 | 11.0 | 11.0 | 8.0 | — | — | — | — | — | — | — | — |
| A.L. 65 M* | Serum | — | Tr | 0 | — | — | — | — | 0 | 3.0 | 1.6 | 1.3 | 0.5 | — | — |
| | Bile | 0 | 5.0 | 0.2 | 0.7 | Tr | 0 | 0 | 0 | 0.7 | 0.4 | 0.3 | Tr | 0 | 0 |
| | Urine | 0 | 33.0 | 36.0 | 33.0 | 16.0 | 0 | — | — | 50.0 | 49.0 | 50.0 | — | 49.0 | — |
| J.F. 61 M | Serum | 0 | 0 | Tr | Tr | 0 | 0 | 0 | — | — | — | — | — | — | — |
| | Bile | 0 | 0 | 0 | 0 | 0 | 0 | 0 | — | — | — | — | — | — | — |
| | Urine | — | 22.0 | 21.0 | 19.0 | 10.0 | 13.5 | — | — | — | — | — | — | — | — |

*The experiment using oral neomycin was repeated with essentially similar results.
†Traces (less than 0.2 μg./ml.).

gastrointestinal tract of the germ-free animals. In contrast, another group of investigators found lower serum cholesterol levels in germ-free rats than in the conventionally reared animals.[31] Forbes et al.,[32] however, found no significant difference between the serum cholesterol concentration of the germ-free and conventional chickens. Gustafsson et al.[33] demonstrated that after the administration of labeled cholic acid to germ-free rats, only taurocholic acid was present in the feces, instead of a variety of compounds, and they obtained similar results in conventional animals by the feeding of antibacterial drugs. The half-life of cholic acid was considerably increased in the germ-free rats, with a larger pool than in conventional animals.[34] Goldsmith et al.[35] have confirmed the cholesterol-lowering effect of orally administered neomycin in man, and reported a three- to four-fold increase in fecal excretion of bile acids.

These series of findings suggest that changes in the intestinal bacterial flora might influence sterol metabolism and the turnover of bile acids, which in turn may exert an effect upon the metabolism of cholesterol. Several factors may influence the concentration of serum cholesterol in man. If the character of the intestinal bacterial flora is one of them, the well-known epidemiologic data, concerning differences in serum cholesterol levels among different populations of various parts of the world, may be due, in part, to differences in the intestinal flora. Environmental factors, such as diet, water supply, general hygienic conditions etc., are known to cause modifications in the character of intestinal bacteria, and thus would influence the concentration of serum cholesterol.

## Summary

The serum cholesterol concentrations of 56 patients were studied in 112 experimental periods following the administration of neomycin and a variety of antibacterial drugs. Additional studies on the mechanism of the serum cholesterol-lowering effect of neomycin were performed.

The oral administration of neomycin for 4 to 37 weeks, in daily doses of 1.5 or 2 Gm., significantly reduced the mean serum cholesterol concentration in each of 30 patients by 14 to 29 per cent (average, 21 per cent). Serum cholesterol concentrations remained low for the duration of neomycin administration, and returned to control levels after the drug was discontinued. In 10 patients the

esterified fraction of cholesterol and the concentration of phospholipids decreased in the serum in proportion to total cholesterol and the distribution of cholesterol between the alpha- and beta-lipoproteins remained unchanged during neomycin administration.

Combination of oral neomycin with mandelamine, phthalylsulfathiazole, isoniazid, oxytetracycline, and tetracycline did not influence the lowering effect of neomycin on serum cholesterol levels.

Serum levels of neomycin after intramuscular injections of 60 mg. in 10 subjects averaged 12 times higher concentrations than was produced by the oral administration of 2 Gm. of neomycin. The intramuscular administration of 60 mg. of neomycin daily to 10 patients for 3 weeks failed to alter serum cholesterol concentrations. This suggests that the cholesterol-lowering effect of neomycin depends upon its action in the gastrointestinal tract.

The concentration of neomycin was serially determined in the bile, serum, and urine of four patients. Biliary concentrations were higher, or of the same order of magnitude, after intramuscular than after oral administration of the drug. Therefore enterohepatic circulation of neomycin is unlikely.

Radioactive fat-absorption tests following the reduction of serum cholesterol by long-term oral administration of neomycin showed that the absorption of dietary fats was normal in two patients and delayed but complete in two other subjects, suggesting that the cholesterol-reducing activity of neomycin is not dependent on its effect on absorption of dietary fats.

The daily oral administration for 5 to 23 weeks of 8 to 12 Gm. of para-aminosalicylic acid to 15 patients lowered serum cholesterol concentrations significantly in each experiment by 14 to 44 per cent (average: 26 per cent), whereas daily doses varying between 2 and 6 Gm. reduced cholesterol less markedly. The daily addition of 2 Gm. of oral neomycin to high doses of para-aminosalicylic acid did not result in further lowering of serum cholesterol concentrations.

The administration of neamine (500 mg. daily), kanamycin (1 Gm. daily) and chlortetracycline (1 or 1.5 Gm. daily) lowered serum cholesterol concentrations, although less markedly than neomycin or para-aminosalicylic acid.

The oral administration of phthalylsulfathiazole, isoniazid, penicillin, dihydrostreptomycin, oxytetracycline, chloramphenicol, polymyxin, erythromycin, novobiocin, bacitracin, and viomycin failed to alter serum cholesterol concentrations.

The possible role of the intestinal bacterial flora in the cholesterol-lowering effect of neomycin and other antibacterial drugs, and the general relationship of intestinal bacteria to cholesterol metabolism, were discussed.

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# Urinary Aldosterone and Hypertension

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A POSSIBLE ETIOLOGIC ROLE of the adrenal cortex in the genesis of clinical hypertension has been recognized since Goldblatt's demonstration in 1937 that adrenalectomy prevents the expected development of hypertension following bilateral renal artery constriction.[1] Recently, interest in this possibility has been intensified by reports that some hypertensive patients excrete[2-6] and secrete[7] increased amounts of aldosterone in the absence of any apparent known cause.

The following case report describes a hypertensive patient with increased urinary aldosterone attributable to renal sodium wasting, detectable only by severe sodium deprivation. Intensive antihypertensive therapy was associated with improved renal function and a fall in average urinary aldosterone.

### Methods for Metabolic Studies

In collection of urine each voiding was immediately refrigerated. At the end of each collection period the total quantity excreted was frozen until analysis. Sodium and potassium contents of serum and urine were determined in duplicate with a Baird flame photometer with lithium internal standards. Serum chloride was determined by a modification of the method of Asper, Schales, and Schales.[8, 9] Serum and urine creatinine were determined by the method of Bonsnes and Taussky[10] as modified by Brod and Sirota.[11] "Creatinine clearances" were calculated in the usual way from the creatinine content of a 24-hour urine collection and the serum creatinine concentration of the morning of the same day.

The method used for measuring aldosterone[6] was as follows: A 24-hour collection of urine was acidified to pH 1 and allowed to stand 24 hours at room temperature to hydrolyze aldosterone conjugate. The free aldosterone was extracted with chloroform, and the chloroform was evaporated to dryness after suitable washing. The dry steroid residue was chromatographed on paper in toluene saturated with propylene glycol. That part of the residue which migrated with cortisone was recovered and acetylated. The aldosterone diacetate was then freed from other steroid acetates by chromatography on paper in hexane saturated with propylene glycol. The aldosterone was quantitated by ultraviolet spectrophotometry. Normal values in this laboratory are: mean 9.1 ± 2.8 micrograms (standard deviation) per 24 hours.

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### Case Report

R. McK., V.A. no. 2029, a 44-year-old white male, rubber factory worker, was admitted to Crile Veterans Administration Hospital on August 18, 1958, with complaints of morning headache, asthenia, and intermittent tingling of the soles of the feet of 8 to 10 months' duration.

He had been seen by a physician at intervals during 1957 for treatment of asthmatic bronchitis. Blood pressure was within normal limits at that time. The first significant hypertension was observed in June 1958, at which time a value of 158/98 mm. Hg was recorded.

Past medical history included a penile ulcer in 1939, treated with injections, and *Plasmodium vivax* malaria, incurred during World War II in the Pacific Theatre. Routine urine analyses in 1946 and in 1957 had shown no abnormalities.

Important findings on admission in August 1958 were blood pressure 230/120 mm. Hg, barely palpable spleen and liver, and ophthalmoscopic finding of bilateral scattered flame hemorrhages, "cotton wool" exudates, and arteriovenous nicking with mild right papilledema. Occasional wheezes and coarse rhonchi were heard at both lung bases. Cervical venous distention was not present. Cardiac borders were percussed within normal limits. Ankle edema was absent. Congestive failure was considered absent at this and at subsequent examinations. Lung findings, which were inconsistent, were attributable to asthmatic bronchitis. Slight hepatosplenomegaly was considered the result of malaria.

Laboratory findings were hematocrit value 49 per cent and white blood cells 10,500/ml. Of 11 random urine examinations made during this hospitalization, 10 showed a specific gravity of less than 1.010; one was reported as 1.012. Proteinuria

**Table 1**

*Serum Electrolytes Preceding and Following the Convulsion of August 20, 1958*

| Date | Na mEq./L. | K mEq./L. | Cl mEq./L. | $CO_2$ mEq./L. | Intake supplement (mEq) Na | K | Cl | Chlorothiazide |
|---|---|---|---|---|---|---|---|---|
| Aug. | | | | | | | | |
| 19 | | 3.6 | 90 | 28.5 | | | | |
| 20 | | | | | 310 | | 310 | 0.5 Gm. t.i.d. |
| 21 | 132 | 3.0 | 81 | 31 | 155 | | 155 | 0.5 Gm. t.i.d. |
| 22 | 127 | 2.4 | 79 | 27.2 | | 54 | 54 | 0.5 Gm. |
| 23 | 121 | 3.0 | 72 | 34 | | | | |
| 24 | | | | | | | | |
| 25 | 124 | 3.1 | 77 | 36 | | 72 | 72 | |
| 26 | 127 | 5.3 | 89 | 32 | 155 | 40 | 195 | |
| 27 | 130 | 3.6 | 89 | 31.5 | 155 | | 155 | |
| 28 | 129 | 3.4 | 98 | 29.5 | 155 | | 155 | |

ranged from 0 to 2 plus without significant cellular elements. Maximum specific gravity attained in the Fishberg concentration test (15 hours water deprivation) was 1.008 on two occasions. Urea clearance was 87 per cent of normal with blood urea nitrogen 7 mg./100 ml. Divided renal function tests showed bilateral appearance of indigo carmine in 3 minutes and bilaterally similar excretion of sodium, potassium, and chloride. Retrograde pyelography showed no significant abnormality. Chest x-ray showed a cardiac silhouette within normal limits and no significant lung pathology. The electrocardiogram suggested slight left ventricular hypertrophy. Phentolamine methanesulfonate, 5 mg. by rapid intravenous injection, caused no significant fall in blood pressure. Cephalin flocculation was reported negative, prothrombin time within normal limits, total serum protein 6.4, albumin 3.7, and globulin 2.7 Gm./100 ml. Bromsulfalein retention was 6 per cent in 45 minutes. During this hospitalization, the right gastrocnemius muscle and lymph node biopsies were negative. The L. E. test and the serologic test for syphilis were negative.

On the second hospital day, August 20, 1958, the patient had a generalized clonic-tonic convulsion. Skull films showed no abnormality. Ventriculography performed 5 days later was within normal limits, and cerebrospinal fluid obtained at that time contained 23 mg./100 ml. of protein. Electroencephalography 2 days and 21 days after the seizure showed symmetrical, mild, diffuse abnormality.

The presence of headache, severe hypertension, and papilledema suggests that the convulsion was symptomatic of cerebral edema and hypertensive encephalopathy. No additional convulsions or episodes of encephalopathy have occurred.

On the day of the convulsion, August 20, chlorothiazide, 0.5 Gm. at 8-hour intervals, was begun. It was discontinued the second day following the convulsion, a total of 3.5 Gm. having been given. In the 5 days following the seizure, the patient ate but little, and fluid and electrolyte were given by intravenous infusion. The ward diet offered was estimated to contain 100 to 140 mEq. of sodium daily. In table 1 are shown serum electrolyte concentrations, known intravenous and oral electrolyte intake, and medication. (Dietary electrolyte is not known and not included.) In the first 3 to 4 days after the seizure there was a marked fall in serum sodium, potassium, and chloride and a rise in carbon dioxide combining power. The appearance of hyponatremia on August 23, despite an intake of at least 465 mEq. of sodium in the preceding 3 days, suggested a possible disorder of renal or endocrine electrolyte regulatory mechanisms.

Table 2 shows urinary aldosterone values obtained between September 11, 1958, and March 1, 1959. Also shown are chlorothiazide and dietary potassium supplements. During the entire period the patient was in the hospital with the exception of the intervals October 25 to December 8, 1958 and February 5 to 15, 1959. It can be seen that in six specimens examined, three aldosterone values were definitely elevated and one was borderline. No clear correlation with potassium intake or chlorothiazide administration is apparent.

During this hospitalization therapeutic trials of different combinations of chlorothiazide, reserpine, and mecamylamine hydrochloride were made without sustained reduction of blood pressure.

On March 19, 1959, the patient was transferred to the Metabolic Division of University Hospitals of Cleveland for study of sodium and potassium metabolism.

Complaints of headache and malaise persisted. Important physical findings were blood pressures of 225/110 and 270/160 mm. Hg in the left arm

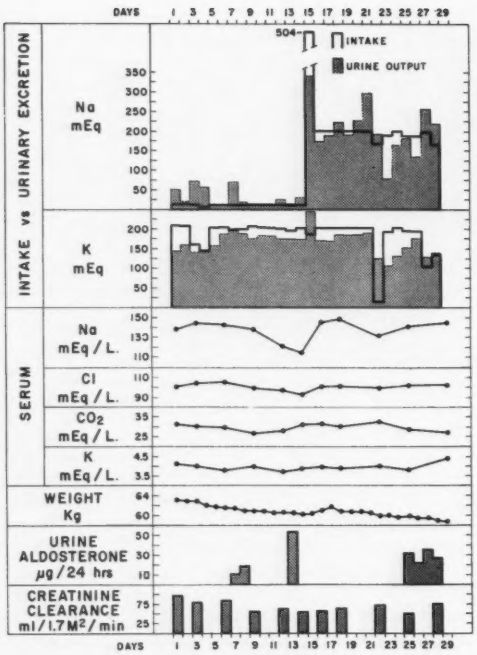


**Figure 1**

*Metabolic studies conducted March 23 to April 20, 1959, showing development of hyponatremia, reduced "creatinine clearance," and increased urine aldosterone during 14 days of sodium intake restricted to 13 mEq. daily. After restitution of serum sodium by hypertonic saline infusion and increase of dietary sodium to 200 mEq. daily, 2 days of negative sodium balance resulted in a second fall of serum sodium.*

and right thigh, respectively. Eyegrounds showed arterial narrowing and tortuosity and fluffy exudates in both eyes, with blurring of the right disk margin. The liver edge was barely palpable, smooth, and nontender.

Laboratory examinations revealed 3 plus proteinuria, 4.83 million erythrocytes per ml. of blood, hemoglobin 13.9 Gm./100 ml., reticulocytes 1.1 per cent of erythrocytes, and leukocytes 6,500/ml. A chest x-ray was within normal limits, and the electrocardiogram showed left ventricular hypertrophy.

On March 23, 1959, metabolic studies were begun with a daily intake of 13 mEq. of sodium and 200 mEq. of potassium. All medication had been discontinued on February 19 except codeine for headache. All food consumed by the patient was from analyzed single lots. Dishes were rinsed after each meal and rinsings were drunk. Figure

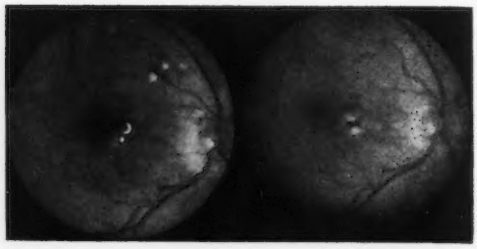

**Figure 2**

*Photographs of right retina in September 1958* (left) *and January 1960* (right) *showing disappearance of exudates and papilledema and resorption of hemorrhages following reduction of blood pressure.*

1 shows the results of these studies. With a sodium intake of 13 mEq. per day, urinary sodium consistently equaled or exceeded sodium intake. There was a progressive fall of serum sodium to 114 mEq. on the fourteenth day. At this time the patient was not clinically dehydrated but was apathetic and expressed salt craving. On the fifteenth day of study 300 mEq. of sodium were given intravenously as 5 per cent sodium chloride, and dietary sodium was increased to 200 mEq. by the addition of enteric-coated sodium chloride tablets to the otherwise unchanged diet. Marked sodium retention was observed on the first day only of increased sodium intake and thereafter the patient appeared to be in approximate sodium balance.

On the twenty-first and twenty-second days, severe headache was associated with negative sodium balance and reduced serum sodium concentration. Although the sodium deficit was apparently rapidly repaired, urinary aldosterone was still elevated 6 days later.

Renal potassium excretion was not remarkable at any time. (Kaliuresis induced by hypertonic saline infusion (study day 15) has been previously described in normal persons.[22]) The progressive fall in creatinine clearance with sodium deprivation has been described in normal persons and has been attributed to reduced plasma volume.[18] Consistent changes in blood pressure were not observed at any time during these studies.

On May 20, 1959, the patient was returned to Crile Veterans Administration where he was equipped with, and trained in the use of a sphygmomanometer. Vigorous antihypertensive therapy was initiated. On June 3, 1959, he was discharged to the home of his sister with instructions to take 2.0 Gm. of sodium chloride daily with an ad lib. diet, reserpine 1.0 mg. daily, and mecamylamine hydrochloride as required to regulate blood pres-

**Table 2**

*Urine Aldosterone, September 11, 1958 to March 1, 1959*

| | 9-11-58 | 9-29-58 | 10-17-58 | 10-18-58 | 10-19-58 | 3-1-59 |
|---|---|---|---|---|---|---|
| Urine aldosterone μg./24 hrs. | 39 | 31 | 7 | 11 | 21 | 14 |
| Chlorothiazide Gm./day | 0 | 0 | 1.5 | 1.5 | 1.5 | 0 |
| Potassium supplement mEq./day | 50 | 0 | 80 | 80 | 80 | 0 |

sure. In this environment, he was able to maintain his systolic blood pressure at approximately 160 mm. Hg and experienced relief of headaches and an improved sense of well-being. After six months in the home of his sister, he moved to his father's home where he soon began to experience difficulty in controlling his blood pressure. On February 15, 1960, he was admitted to Crile Veterans Administration Hospital for re-evaluation. All medication was discontinued on admission.

During the first week following admission, blood pressure ranged from 230/120 to 180/100 mm. Hg. Remarkable improvement in the appearance of the eyegrounds had occurred. Figure 2 shows photographs of the right retina taken shortly after the first admission in August 1958 and the appearance of the same eye in February 1960. Papilledema, hemorrhages, and exudates had disappeared completely. Equivalent changes had occurred in the left eye. The only observed evidences of retinopathy were bilateral segmental arteriospasm and postpapilledema halo in the right eye. The remainder of the physical examination was unchanged.

Routine blood examinations were within normal limits. Urine analysis revealed a trace of albumin and occasional red and white cells in the centrifuged sediment. Serum sodium was 137 mEq./L., potassium 4.3 mEq./L., chloride 99 mEq./L., and carbon dioxide combining power 25 mEq./L. Urea clearance was 108 per cent of normal with blood urea nitrogen 12 mg./100 ml. The maximum specific gravity attained in the Fishberg concentration test (15 hours water deprivation) was 1.022 on one occasion and 1.020 on a second occasion. Of random urine specimens examined during this hospitalization, 41 per cent had specific gravities of 1.010 or less; 53 per cent had specific gravities greater than 1.010 and less than 1.016; and 6 per cent had specific gravities of 1.016 or greater, in contrast to the consistent hyposthenuria of the first admission.

Urinary aldosterone values were 3.8, 7.1, and 6.5 μg. per 24 hours on March 7, 8, and 9 respectively, while the patient was taking the ward diet estimated to contain approximately 100 to 140 mEq. of sodium daily, without dietary electrolyte supplementation. These hormone values appear to be clearly different from those obtained on the first admission (table 2) on the same diet.

On March 22, 1960, the ward diet was changed to one having a calculated sodium content of 18 mEq. per day. This diet was continued for 28 days. During the first 12 days, daily urinary sodium excretion gradually decreased from an initial 122 mEq. to values generally less than 18 mEq., with occasional values as high as 23 mEq. and as low as 6 mEq. Serum sodium during the 28-day period ranged from 131 to 147 mEq./L., without regular pattern. On the twenty-eighth day the value was 137 mEq./L. Urinary potassium ranged from 41 to 91 mEq. daily, averaging 62 mEq.; serum potassium ranged from 3.8 to 5.0 mEq./L.

Although a rather long period was required to reduce urinary sodium excretion below intake, the patient was able to remain in sodium balance and to avoid hyponatremia for a prolonged period with a daily intake of only 18 mEq. This test of ability to maintain sodium balance with a low intake, while not precisely comparable to the study performed 1 year earlier, suggested an improved capacity for sodium retention.

## Discussion

These data suggest the following sequence of events: In 1958, for unknown causes, the patient developed severe hypertensive disease with renal dysfunction characterized by loss of concentrating ability, proteinuria, and a tendency to renal loss of sodium. The tendency to sodium loss was compensated by increased aldosterone secretion, permitting maintenance of sodium balance with normal sodium intake. When sodium intake was reduced to 13 mEq. daily, however, a consistently negative sodium balance developed, leading eventually to hyponatremia (study days 1 through 14, fig. 1). This result occurred despite an apparent marked rise in

aldosterone secretion and a reduction of glomerular filtration. Significant amounts of sodium persisted in the urine despite the presence of hyponatremia. When daily sodium was increased to 200 mEq., balance was restored, though only minimal sodium retention occurred. Thereafter, a brief period of negative sodium balance (study days 20, 21, and 22, fig. 1) resulted in a fall of serum sodium to near hyponatremic levels.

Following these metabolic studies, there occurred a remission of the disease process, possibly the result of therapy. This remission was manifested by improved appearance of the eyegrounds (fig. 2) and improved renal function, shown by return of concentrating ability. Renal sodium conservation seemed improved as shown by the failure to develop hyponatremia during 28 days of low-sodium intake. Urinary aldosterone was well within normal limits when the diet contained an amount of sodium that previously had been associated with hyperaldosteronuria.

The hyponatremic syndrome described in this patient is clearly different from the hyonatremic syndrome attributed to "inappropriate secretion of antidiuretic hormone" by Schwartz, Bennett, Curelop, and Bartter,[12] and is presumably of renal origin. The patients described by those authors did not lose weight as sodium loss continued, reflecting maintenance of extracellular volume. In our patient, sodium loss was accompanied by weight loss and decreased "creatinine clearance," reflecting reduction of extracellular volume.

In summary, it is postulated that this patient had the clinical sydrome of severe hypertension, associated with a renal sodium-losing tendency compensated by increased aldosterone secretion. Pharmacologic reduction of blood pressure was followed by improved renal function and ameloriation of the tendency to sodium loss. A consequent reduction of aldosterone secretion was reflected in reduced urinary aldosterone.

The course of this patient suggests a possible explanation for the otherwise unexplained increase in aldosterone excretion[2-6] and secretion[7] observed in some hypertensive patients. It is unlikely that such findings reflect an idiopathic physiologically excess secretion of aldosterone as a sole etiologic agent in the genesis of hypertensive disease. The usual absence in hypertensive patients of the definite potassium deficiency, and alkalosis characteristic of Conn's syndrome[13] suggests that increased aldosterone secretion in hypertension is secondary and compensatory.

The hypothesis is suggested that the increased aldosterone secretion occurring in some hypertensive patients is compensatory to a renal sodium-losing tendency. Validation of this hypothesis requires a demonstration that increased aldosterone secretion in hypertensive patients is usually associated with a renal sodium-losing tendency. Such evidence is neither available nor easily obtained, for if aldosterone compensation were effective, hyponatremia would not be produced except by very low sodium intakes over quite long periods of time, particularly if marked falls in glomerular filtration rate occurred.

The hypothesis is supported, however, by evidence that a renal sodium-losing tendency occurs with significant frequency in hypertensive patients.

Frank "sodium wasting nephritis" characterized by evidence of severe renal disease and hyponatremia with fairly high sodium intakes has been described in association with hypertension.[14-16] A less obvious disorder was observed by Newborg and Kempner[17] in a series of 159 patients with malignant hypertension treated with a rice-fruit diet (less than 7 mEq. of sodium daily). Of these patients, 20 per cent developed hyponatremia or hypochloremia of a degree sufficient to warrant modification of the diet. The authors comment that "inability to conserve electrolytes may, in some instances, be the chief manifestation of renal dysfunction and may occur in the absence of severe impairment of PSP excretion or of marked azotemia."

Several investigators have observed that, statistically, hypertensive patients excrete more sodium during and immediately following a standard infusion of hypertonic saline

than do normotensive persons.[18-23] This phenomenon is consistent with the postulate that the diseased kidneys of some hypertensive patients tend to excessive losses of sodium but such patients are prevented from developing a persistently negative sodium balance over a wide range of sodium intake by a compensating increase in aldosterone secretion. Since hypertonic saline infusion reduces aldosterone secretion,[24] an aldosterone-compensated renal tendency to sodium-losing may become evident after such infusions.

The reported tendency of hypertensive persons voluntarily to ingest more sodium chloride[25, 26] than normotensive persons is also consistent with a sodium-losing tendency.

### Conclusion and Summary

A 44-year-old man with severe hypertension, hypertensive retinopathy, hypertensive encephalopathy, and loss of renal concentrating power was observed to have hyperaldosteronuria. Dietary sodium restriction revealed a renal sodium-losing tendency. Intensive therapy designed to reduce blood pressure was followed by improvement in eye-grounds, return of renal concentrating power, improved renal sodium-retaining power, and decreased urinary aldosterone excretion.

It is suggested that the hyperaldosteronuria of some hypertensive patients is a manifestation of an aldosterone-compensated renal sodium-losing tendency.

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Now the properties of water have the result that more readily than other substances it exists simultaneously and in large quantities in the three phases of solid, liquid, and gas as ice, water, and aqueous vapor. This depends upon the high latent heats of fusion and vaporization, the high freezing point of water, and its vapor tension. Water enhances the complexity of the environment, and is one principal factor in the mobility of the environment as a whole. Further, it makes for stability; other things being equal, the greater the number of phases, the less the tendency to change. Among phases the disperse colloidal type is unique and of very great importance—almost the sole basis, indeed, of great physical complexity—and, as above shown, the peculiar properties of water highly favor the colloidal condition.

The solvent power of water much increases the number of components which may enter into a system of which it is a part; hence the large number of components of sea water, blood plasma, etc. The variety of compounds, both organic and inorganic, which contain carbon, hydrogen, or oxygen also causes enormous increase in the number of components of biological systems like protoplasm.

The specific heat of water, its latent heats of fusion and vaporization, and the high freezing point all contribute to the restriction of temperature range within the organism, in the waters, and over the whole surface of the earth. The vapor pressure of water has been shown to possess great and exceptional variability with change of temperature. This is the most important property of water meteorologically, and is the necessary condition for its ample circulation. The ratio between the gas pressure of carbonic acid and its concentration in water (absorption coefficient) has been shown to be the great factor in establishing the mobility of that substance.—LAWRENCE J. HENDERSON. *The Fitness of the Environment.* New York, The Macmillan Co., 1924, p. 258.

# Familial Idiopathic Cardiomegaly

*By* WAYNE H. SCHRADER, M.D., GEORGE A. PANKEY, M.D., RICHARD B. DAVIS, M.D., AND ATHANASIOS THEOLOGIDES, M.D.

AMONG CAUSES of cardiac enlargement of obscure origin that confront the clinician and pathologist alike are subendocardial fibroelastosis, inflammatory myocardiopathies, glycogen-storage disease, amyloidosis, muscular subaortic stenosis,[1] asymmetrical hypertrophy of the heart,[2] idiopathic myocardiopathy,[3] and familial cardiomegaly. Familial cardiomegaly, originally named in 1949 by Evans,[4] has been the subject of many communications, primarily in the European literature, but it is little better understood now than after the original report. Various theories to explain the cardiomegaly include cardiac involvement with toxoplasma[5] and trypanosomiasis, a myocardiopathy similar to that seen in Friedreich ataxia but without neurologic involvement,[4] glycogen-storage disease, and an inheritable disorder of the myocardium transmitted as a Mendelian dominant,[6] with sex linkage.[7] Similar to the enigma of causation, the question of the specificity of the clinical picture and of the autopsy findings has been controversial with a familial occurrence being the only unequivocal common denominator. Unfortunately, relatively little emphasis has been devoted to the character and specificity of the morphologic findings, with the majority of reports having appeared in clinical literature.

It is the purpose of this paper to present the clinical and necropsy studies of two sisters who died in young adulthood of progressive cardiac disease. Family history and the significance of specific anatomic findings are discussed with a few remarks regarding etiology.

## Case Reports

### Case 1

This 21-year-old white girl was well until age 17 years, when she noticed nervousness, tremor of the hands, and a "throbbing" in her neck. At age 18½ years she was told her heart was enlarged, and she received digitalis for 2 months. At age 20 she noticed decreased effort tolerance. In January 1949, at age 21 years, she was hospitalized for dyspnea and hemoptysis. Two sputum cultures were positive for tubercle bacilli, but the diagnosis of tuberculosis was not further substantiated. In March 1949 she noticed ankle swelling.

There was no history of scarlet fever, acute rheumatic fever, chorea, or tonsillitis. Vertigo and cyanosis had not been present in her childhood years, and she had tolerated an appendectomy at age 15 without difficulty.

Abnormal findings were limited to the heart, which was enlarged both to the left and to the right. Ectopic ventricular beats were heard but there were no murmurs.

Electrocardiograms showed left axis deviation and an accelerated atrioventricular conduction pattern suggestive of Wolff-Parkinson-White syndrome. A diagnosis of idiopathic cardiac hypertrophy was made at cardiac fluoroscopy. A complete blood count, erythrocytic sedimentation velocity, and basal metabolism rate were all normal.

The patient gained weight (from 114 to 134 pounds) despite digitalization. On one visit to the clinic jaundice with hepatomegaly was noted. On July 1, 1949, she had an episode of syncope.

On August 19, 1949, she was admitted to the University of Minnesota Hospitals with severe congestive heart failure. She also gave a history of occasional hemoptysis and had noted swelling of the right arm. Physical findings included a pulse of 110, blood pressure of 90/70, and temperature of 98.6 F. At this time a gallop rhythm was noted at the apex but again no murmurs were audible. Physical findings in the right upper extremity were suggestive of thrombophlebitis of the axillary vein.

On August 20, 1949, the patient had a grand mal seizure following an intravenous injection of aminophylline. The patient's congestive heart failure failed to respond, she became semicomatose, and died on September 8, 1949.

At necropsy there was moderate pitting edema of the lower extremities and slight cyanosis of the lips and nailbeds. Approximately 1 liter of clear straw-colored fluid was present in each pleural space and in the peritoneal space, and 50 ml. were in the pericardial sac. No pleural or pericardial adhesions were present.

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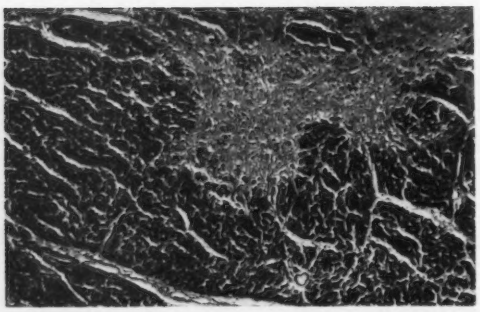

**Figure 1**

*Case 1. Section from left ventricle showing a typical area of loose fibrosis surrounded by intact myocardium. Hematoxylin and eosin stain.*

The heart weighed 400 Gm. and was globular in shape. The epicardial surface was pale gray and firm, grayish nodules were present that extended into the myocardium and were surrounded by muscle of softer-than-normal consistency. The thickness of both ventricular walls varied markedly. The very dilated right ventricle measured 2 to 3 mm. anteriorly near the apex and was 5 mm. in other areas. The left ventricular wall varied from 5 to 15 mm. and revealed diffuse patchy fibrosis. The interventricular septum likewise showed rather marked, fine, patchy fibrotic change. In the thinned areas the fibrosis was much more evident. Underlying the fibrotic area of the left ventricle was a mural thrombus. Remaining endocardium, valves, and coronary arteries were unremarkable.

The lungs were heavy, weighing 470 and 425 Gm. each. Several wedge-shaped fresh pulmonary infarcts were noted in each lung, but no large pulmonary emboli were found. The lungs exuded bloody fluid when cut. In the right lower lobe were several small, white, nodular areas surrounding a 1-cm. subpleural firm nodule. This nodule contained a thick white fluid in its central portion. No lymphadenopathy was noted.

The liver weighed 1,600 Gm. and grossly revealed the pattern of severe passive congestion. The kidneys and spleen were unremarkable except for several depressed fibrotic areas over their surfaces.

In the right superior parietal area of the brain, a 1.5-cm. circumscribed, firm area was noted with petechiae scattered through it. Other portions of the brain and remaining organs were unremarkable.

On microscopic examination multiple sections of myocardium stained with hematoxylin and eosin showed severe muscular degeneration with early fibrous replacement in many areas (fig. 1). Hypertrophy, with pallor, granularity and vacuolization of the muscle fibers, was noted. The nuclei were often swollen or pyknotic and of bizarre shape (fig. 2). A few scattered small mononuclear cells were present in areas of degeneration. A periodic acid-Schiff stain for glycogen in the myocardial vacuoles revealed only very minimal positive material. A Giemsa stain of some sections revealed no toxoplasma.

The cerebral and pulmonary lesions proved to be typical granulomatous reactions with central necrosis, and epithelioid and Langhans' giant cells. An acid-fast stain of the lung revealed no organisms, however. Pulmonary infarcts were present, and sections of liver and spleen showed passive congestion. The remainder of the microscopic examination was normal.

**Case 2**

This patient, a 17-year-old sister of case 1, gave a history of easy fatigability of many years' duration. At age 12 years cardiomegaly was noted on a routine chest x-ray. At age 14 she began to have mild exertional dyspnea, which progressed slowly over the next 3 years. Congestive heart failure was diagnosed and treated with digitalis, low-salt diet, and diuretics. She also noted vertigo but had no syncopal episodes. There was no history of cyanosis or rheumatic fever.

On physical examination abnormal findings included pulsating neck veins, cardiomegaly without murmurs, protodiastolic gallop rhythm, and hepatomegaly. The clinical impression was familial myocardiopathy.

Electrocardiograms revealed a typical Wolff-Parkinson-White syndrome. Complete blood count, erythrocytic sedimentation rate, and urinalysis were normal. The patient responded to treatment with digitalis and diuretics, and quinidine was given to prevent arrhythmias.

Three weeks later, on November 6, 1959, the patient was hospitalized because of increasing congestive heart failure and episodes suggestive of paroxysmal supraventricular tachycardia.

Physical findings were essentially unchanged with the exception that posterior basilar rales and pedal edema were noted. Again a protodiastolic gallop rhythm was heard, but no murmurs were audible. During her hospitalization the patient became jaundiced. She also had symptoms of a schizophrenic reaction. Treatment for her congestive heart failure was without success and she died on December 2, 1959.

At necropsy 3,000 ml. of clear straw-colored fluid were removed from the pleural spaces, 2,000 ml. from the peritoneum, and 100 ml. from the pericardial sac.

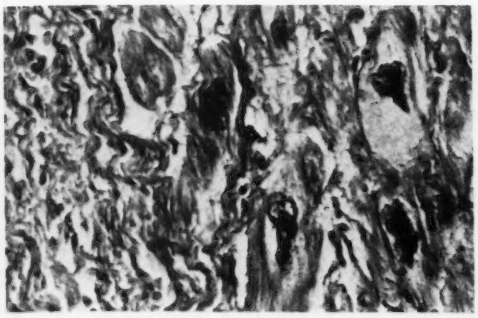

**Figure 2**

*Case 1. Section from periphery of fibrotic area seen in figure 1. Note the degenerating, pale, finely vacuolated muscle cell near the upper margin. Giant bizarre nuclei are also present in the muscle cells. Hematoxylin and eosin stain.*

**Figure 3**

*Case 2. Opened left ventricle showing marked thickening of ventricular wall and small mural thrombus designated by an arrow. Also note the slightly thickened endocardium which appears very fibrous here due to lighting artifact.*

The heart was globular and massively enlarged to 920 Gm. No pericardial adhesions were present. The ventricular walls were thickened. The left ventricular wall varied in thickness from 20 to 25 mm., and the right ventricular wall measured 10 mm. at its thickest cross section (fig. 3). Dense white fibrous bands extended through the left and right ventricles. The interventricular septum revealed severe fibrous replacement. No evidence of acute necrosis or gross areas of removal of necrotic muscle were found. The remaining myocardium was pale and somewhat soft. No fibrosis of atrial muscle was evident grossly. The endocardium of both ventricles was mildly thickened, but even after formalin fixation it did not appear like subendocardial fibroelastosis. Fresh-appearing mural thrombi were seen in both ventricles. Examination of valves and of coronary circulation revealed no congenital or acquired abnormalities.

Weights and appearances of lungs, liver, and spleen were characteristic of severe acute and chronic passive congestion. A small fresh infarct of the left kidney was also present. The remaining organs were grossly normal.

Microscopic examination of left ventricular tissue revealed massive replacement of structure by dense bands of fibrous connective tissue (fig. 4). Remaining muscle fibers were often pale and granular or contained clear vacuoles of irregular shape and size. Their nuclei were often of unusual size and shape, and occasional giant nuclei were noted. A mild mononuclear infiltrate was seen in only a few sections. In the right ventricle and atria only the loose early fibrotic change and severe vacuolization were present. The sections of interventricular septum revealed dense hyaline scar. Special stains were negative for amyloid with methyl violet, negative for fat with Sudan stains, negative for glycogen with Best's carmine, and negative for toxoplasma and other organisms with Giemsa stain.

Mural thrombi were verified on microscopic examination of both ventricles. The endocardium was not remarkably altered in any area.

Sections of lungs, liver, spleen, and pancreas showed evidence of passive congestion, both acute and chronic. A small fresh infarct was present in the right kidney.

The large cells of the nuclei tuberes laterales of the brain were significantly altered. The neurons were severely swollen, and their distended cytoplasm was filled with faintly eosinophilic granules. Nissl-stained sections showed only faint staining of these granules. Fat stains, periodic acid-Schiff stain, and Bielschowsky stain revealed no abnormal structures. Phosphotungstic acid-hematoxylin stain showed no surrounding glial reaction. This entire appearance is without adequate explanation.*

The family history of these two sisters was extensively studied. Their mother died at age 34, in 1946. She had been hospitalized elsewhere in 1944 for "myocardial heart disease and asthma."

*These sections were examined by Dr. L. J. Rubinstein of the London Hospital Medical College and by the Armed Forces Institute of Pathology. It is their opinion that no similar abnormality has previously been reported in the literature.

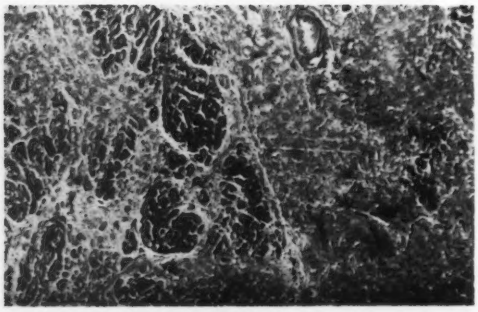

**Figure 4**

*Case 2. Section from left ventricle showing dense fibrosis surrounding retained islands of myocardium. This is representative of left ventricular myocardium. Hematoxylin and eosin stain.*

In 1946 she was rehospitalized and a diagnosis of "myocarditis" was made. She was discharged with a poor prognosis and died at home. No autopsy was obtained. One brother of the sisters died at age 16, when he was hit in the anterior chest by a baseball. He had been well prior to that time.

The patient's father, age 54, two sisters, age 28 and 30, one brother, age 15, and all five nieces and nephews, age 2½ to 9 years, were examined. In no case was there any history suggestive of heart disease. Physical examination, electrocardiogram, and x-ray studies of the heart failed to show any abnormalities except that the father was slightly hypertensive. One brother, age 20, was not available for these studies, but he was known to be healthy and there was no history of heart disease.

### Comment

The final, and most complete, classification of disease entities characterized by cardiomegaly must fall to the pathologist. The usual causes of an enlarged heart are well known and need not be dwelt upon here. Reports of idiopathic cardiomegaly have recently become more numerous. This syndrome appears unrelated to any known cardiovascular anomaly or to the aging process. It is characterized by a cardiac demise in a young adult with a large heart and is considered basically a myocardial disease. Autopsy reveals massive enlargement and dilatation of the heart, predominantly left-sided, and with or without fibrosis. Hypertrophy of myocardial fibers with patchy vacuolization and fibrosis is seen microscopically. No evidence of significant endocardial or epicardial abnormality is noted.

Dr. William Evans described an interesting variant of this complex in 1949.[4] The presence of a definite familial tendency was suggested with his presentation of three families with cardiomegaly and symptomatic heart disease. Since that time several other families have been presented as examples of this idiopathic familial cardiopathy. A recent excellent review by Beasley[8] of some 38 cases in 14 families would seem to verify the existence of such an entity. The two cases described in this report along with their family background are offered as further evidence of such a familial disease.

### Clinical Comment

It is apparent that many of the reported cases of familial cardiomegaly had unrecognized heart disease for some years as was documented in our second case. The age of onset of symptoms is highly variable, but is usually between the ages of 5 and 20 years. Dyspnea on exertion, palpitation, giddiness, and syncopal episodes are common symptoms before overt congestive heart failure is manifest.

On physical examination most of these patients appear to be of normal habitus and are well nourished. Abnormal findings include generalized cardiomegaly without a murmur. In those cases that do show murmurs, they most often are of low intensity and questionable significance. No murmurs were heard in either of the two present cases. A protodiastolic gallop or triple rhythm is often heard. As the disease progresses, the signs of left- and right-sided congestive heart failure become increasingly evident. There are no signs or symptoms that are pathognomonic of familial cardiomegaly, however, and the disease may be manifest clinically only by sudden unexplained death.

Useful laboratory studies are limited to the x-ray and electrocardiogram. The former shows generalized cardiomegaly with left-sided preponderance but without pulmonary congestion initially. Electrocardiographic findings are quite varied, but most commonly an

abnormal conduction pattern is found. This may be manifest as intraventricular block (usually left bundle), partial atrioventricular block or as the Wolff-Parkinson-White syndrome. The latter should especially alert the clinician to the possibility of familial cardiomegaly although it occurs in other conditions such as Ebstein's anomaly.[9]

The age at death varies but most reported cases have died before 30 years of age.[10] Death usually results from intractable heart failure or the development of an arrhythmia such as paroxysmal supraventricular tachycardia.

### Pathologic Comment

In comparing the cases presented here with those in the literature one notes the following points.

Hearts of previously autopsied cases have been markedly enlarged, weighing up to 1,134 Gm., with an average of 658 Gm.[8] The 920-Gm. heart of our case 2 certainly would fit in the classification of cardiomegaly, and the smaller 400-Gm. heart, though only moderately enlarged by weight, appeared markedly enlarged owing to dilatation of the chambers. This rather marked difference in weight is unexplained but suggests that a long-term process is involved with heart size possibly dependent on the ability of the patient to withstand the progressive cardiac deterioration. This view is somewhat borne out by examination of the literature, in that cases with the longest history of symptoms also had the largest hearts. This is also true in the present cases with cardiomegaly noted in our second case 5 years prior to demise. Increased weight is not a true indication of heart size, however, and the importance of marked dilatation of the heart has been stressed by many observers.

Fibrosis varied from dense hyaline scar, predominantly left-sided, to loose, more recently developed fibrosis in other areas. The smaller heart was also the least fibrotic and showed much looser fibrosis in the present cases. By Evans' criteria, fibrosis must be present in cases designated as familial cardiomegaly.[4] However, cases discussed in 1942[11] showed no fibrosis, yet were considered as the first recorded examples of this familial entity. Garrett suggested that the disease should be categorized by the presence or absence of fibrosis. He noted that both fibrotic and nonfibrotic cases have not been observed in the same family.[12] Such a superficial distinction has little merit in the face of the similarity of these cases in all other respects. This variable appears to be a manifestation of only one factor, possibly a time factor.

Vacuoles were prominent within muscle fibers in both cases presented. These were noted in islands of retained muscle fibers surrounded by fibrosis and also in the atria and right ventricle where fibrosis was not so marked. Vacuolization has been described both with and without associated fibrosis,[6, 13] and is thought to represent degenerative, possibly ischemic, change in muscle fibers. The contents of these vacuoles do not stain with periodic acid-Schiff, Best's carmine, or fat stains.

Although endocardial disease is not a significant component of this complex, mural thrombosis was present in both of our cases. A high incidence of mural thrombosis and secondary embolization is not noted in previous cases. Flynn and Mann[14] postulated, however, that the dilated ventricle in a failing heart results in decreased emptying and a subsequent decreased oxygen content of blood to nourish endocardial and subendocardial tissues. The damage may result in mural thrombosis and possible Thebesian vein thrombosis.

Etiologic considerations may be divided into four main groups: infectious, allergic, mechanical and chemical, and congenital. The possibility of a myocarditis as the underlying cause of progressive myocardial disease was entertained frequently in discussions of earlier isolated cases of cardiomegaly.[15, 16] With the familial aspects of the syndrome apparent, an infectious etiology has become less attractive, though Sommers[17] presented three cases in a family in all of which enlarged hearts showed active inflammation. Two families described by Paulley et al.[5] showed a high inci-

dence of positive serologic tests for toxoplasmosis as well as high familial incidence of cardiomegaly and cardiac symptomatology. The organism was never isolated, however, by examination of autopsy specimens or by inoculation studies. Doubt has also been expressed[12, 13] that these serologic tests signify toxoplasma infection and over the postulated existence of a special strain involving only myocardium that Paulley has suggested. Multiple microscopic sections from both hearts in the present cases also failed to reveal any toxoplasma pseudocysts. The presence of active tuberculosis in our case 1; in one of Evans' original cases,[4] and in a recent case described by Beasley[8] is of some interest. That these were all recent acute infections is apparent from the descriptions, and most likely are related to the cardiac abnormality only by hastening the patient's inevitable demise. Infection in other recorded cases could hardly be suspected as an etiology without fever, predisposing illness, or microscopic evidence of an inflammatory reaction.

Allergic diseases such as rheumatic fever and the collagen diseases have been considered. The lack of valvular, vascular, or epicardial changes speaks strongly against such a relationship. The general lack of findings in other organs, the absence of fever, joint symptoms, skin lesions, and a predisposing hypersensitivity reaction in association with the cardiopathy are also of importance. Of the collagen diseases, systemic scleroderma has more in common with familial cardiomegaly than any other. Diffuse fibrosis of heart muscle with a lack of inflammatory reaction is noted in both. Both may be associated with clinical heart failure, conduction abnormalities, and radiographic cardiac enlargement. Here the similarity ends, however. Scleroderma heart disease is most common as a part of systemic scleroderma and occurs mainly in the fourth and fifth decades. No specific familial tendency has been noted. Hearts do not undergo the massive enlargement seen in familial cardiomegaly. Fibrosis is more often fine and interstitial in type and does not show the predominant left-sided increase noted in familial cardiomegaly. Microscopic differences are also apparent with a quite cellular and often very vascular fibrous tissue infiltration with secondary muscular degeneration and replacement in scleroderma. Remaining isolated muscle fibers often appear quite normal, despite being surrounded by fibrous tissue.[18] The fibrosis in the present two cases differs markedly from this, and suggests a degenerative myocardial abnormality with a secondary replacement fibrosis.

Mechanical and chemical changes in the heart can also cause cardiomegaly. Absence of hypertension, coronary disease, congenital defects, valvular disease, or electrolyte abnormality rules out a likely relationship in this category.

Recent interest in incomplete subaortic stenosis has been expressed by several authors. A report by Brent et al.[1] described two families with such a clinical entity. All were characterized by cardiomegaly, heart failure, and the presence of heart murmurs. Walther et al.[10] suggested that the progressive familial cardiomegaly with left ventricular hypertrophy may lead to a partial outflow obstruction. Such obstruction could then be a stimulus for further severe hypertrophy. Descriptions of the hearts in most cases of idiopathic cardiomegaly, however, include marked dilatation as well as hypertrophy of the cardiac chambers. This plus the absence of murmurs in a large proportion of patients with familial cardiomegaly would make unlikely a mechanism like subaortic stenosis.

Of interest, also, is the work of McAllen,[19] who cited two cases of longstanding potassium deficiency that resulted in severe diffuse myocardial fibrosis. The hearts were not enlarged significantly, however, and degenerative lesions with necrosis and inflammatory cells could be seen even in the longstanding deficiencies.

Last and most important, is the possibility of a congenital defect of the myocardium. The two most important abnormalities related to cardiomegaly are Friedreich's ataxia and Von Gierke's disease. The latter has been mentioned and discarded by most previous au-

thors because of the following characteristics of Von Gierke's disease that are not found in idiopathic cardiomegaly: Involvement of heart with death prior to 1 year of age; defect in glycogenolysis, i.e., ketosis, hypoglycemia, and abnormal glucose tolerance tests; and massive glycogen deposits in multiple organs on autopsy. Evans found a moderate amount of glycogen in the heart of one of his original cases but thought it was insignificant and could be seen in any degenerative condition such as heart failure.[4] No significant increase in glycogen was found in the present case 2. (Only case 2 was studied with alcohol fixation and Best's carmine stain.)

Friedreich ataxia is often associated with cardiac abnormalities and was suggested by Evans as a related familial congenital abnormality. Electrocardiographic findings in 38 cases of Friedreich ataxia were reported by Evans in an earlier publication, with significant abnormality in 10 of these.[20] Dorothy Russel described myocardiopathy in four cases of Friedreich ataxia at autopsy. Hypertrophy with left predominance, diffuse fibrosis, and scattered degenerative areas with inflammation were present.[21] Familial tendency of Friedreich ataxia is apparent, but no family has been found showing isolated cardiomegaly in one member and Friedreich's disease in another.

Campbell and Turner-Warwick[6] have postulated a genetic basis for idiopathic cardiomegaly and suggested that it is inherited as a Mendelian dominant. Inheritance only through the maternal half of a family has been demonstrated in several two-generation studies,[7] suggesting sex-linked transmission. Although no autopsy study of the mother was made in the family presented here, involvement of the mother's heart by an abnormality of myocardial nature is suggested. Such a family relationship would not offer any proof of a sex-linked transmission, but would fit the general scheme of such a concept.

Of interest is the possible relationship of infantile hypertrophy of the heart to adult myocardial disease. The infantile variety also shows a marked familial tendency but no family has been described showing an adult-infant disease pattern. That the infantile hypertrophic disease is basically myocardial is suggested by the work of Black-Schaffer and Turner.[22] They postulated an abnormal cell division of myocardium, which may result in the loss of efficiency of the myocardium due to shortened fibers. Secondary dilatation and hypertrophy would result, with formation of endocardial fibrosis in some cases. Although a basic shortcoming of adult cardiomegaly as a congenital abnormality is the long latent period, one could still postulate a basic myocardial defect originating in development. Such a concept would necessitate the reaching of "critical size" as described by Linzbach[23] after which marked myocardial change takes place. Whether this change involves an anoxic phenomenon due to progressive hypertrophy and decreased vessel-fiber ratio or is due to a basic myocardial fiber abnormality, possibly enzymatic, with dilatation and degeneration is not known. With present increased interest in histochemical technics, enzymatic studies in subsequent cases may be of real value in clarifying a very cloudy disease complex. In order to accomplish such studies, however, this disease entity must be recognized at the autopsy table or earlier in order that valid metabolic studies be completed.

**Summary**

Two young adult sisters are described with clinical and pathologic findings of myocardial disease. These cases along with a suggestive family history are presented as examples of familial idiopathic cardiomegaly. Pathologic findings are compared and contrasted with those in the literature, and etiologic concepts are discussed. It is concluded that a congenital myocardial abnormality is the most likely etiology and suggestions for further studies are presented.

**Acknowledgment**

We wish to express appreciation to Dr. Jerome Krovetz, of the Pediatric Department, who examined the children in the family under study. We are also grateful to Miss Josephine Walaszek for her technical aid in the preparation of this paper.

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Though old Fort Crawford on the upper Mississippi has vanished, the results of the experiments Beaumont conducted within its walls have come down to us with undiminished luster through more than a hundred years and are an enduring portion of America's gifts to science. "Truth, like beauty," Beaumont wrote, "when unadorned is adorned the most, and in prosecuting these experiments and inquiries I believe I have been guided by its light." Such is the ideal and such is the faith of the frontiersman in science, and in so far as he is loyal to his convictions he will leave behind him, as Beaumont did in his records, lasting contributions from his fleeting years.—Walter B. Cannon, M.D., *The Way of An Investigator.* New York, W. W. Norton & Company, Inc., 1945, p. 29.

# A Method of Treatment for Pericardial Pain

*By* ARTHUR S. WEISSBEIN, Capt., MC, AND FLOYD N. HELLER, Capt., MC

THE USUAL CASE of acute idiopathic pericarditis presents relatively little problem in management, except for the relief of pain during the first few days of illness. Some patients, however, suffer a prolonged and relapsing course, which can result in considerable discomfort, and at times incapacitation. Therapy for this disorder is symptomatic, reliance generally being placed on salicylates, opiates, and sedatives. There are reasons for this. The mechanism of pericardial pain is not understood, making it impossible to provide other than nonspecific modes of relief. Moreover, the discomfort is rarely of sufficient intensity to cause the patient great concern.

We recently encountered a patient in whom the pain of acute pericarditis was so severe and prolonged that frequent doses of opiates were required for alleviation. This patient and a subsequent one received immediate, complete, and long-standing relief from a left stellate ganglion block, a method of treatment that, to the best of our knowledge, has not been previously utilized.

It is hoped that this report might stimulate re-exploration of the much neglected field of the mechanism of pericardial pain. In addition, a trial of this technic would seem worthwhile in the patient with the initial severe pain of acute pericarditis, and more particularly in the individual whose discomfort is recurrent and incapacitating.

## Case Reports

### Case 1

A 46-year-old white woman was admitted in August 1960 to the Medical Service of the Twenty-Eighth General Hospital. Twelve hours previously she had been awakened by severe, crushing, precordial pain, radiating to the neck and into the left shoulder, markedly aggravated by lying supine and with deep respirations. She noted that sitting up and leaning over offered partial relief; salicylates, however, were ineffective.

Temperature on admission was 99.4 F. The patient was extremely uncomfortable with rapid, shallow respirations; a "paradoxical pulse" of 12 mm. Hg was present. Physical examination was otherwise normal.

On admission serum glutamic oxalacetic transaminase was 0 units and serum glutamic pyruvic transaminase was 3 units. A complete blood count including a sedimentation rate was normal. Serial electrocardiograms (fig. 1) confirmed the diagnosis of acute pericarditis. Initial chest x-ray, compared with previous films, showed generalized enlargement of the cardiac silhouette (fig. 2), which returned to normal 2 weeks after admission. Skin tests for histoplasmosis, coccidioidomycosis, and tuberculosis were negative, as were L. E.-cell preparations and measurement of blood urea nitrogen.

Her course was extremely stormy. Initial hospitalization lasted 66 days, and was characterized by almost daily episodes of severe chest pain, incapacitating the patient and necessitating frequent doses of opiates. A transient friction rub was noted on the fourth day of hospitalization. All attempts to increase the patient's activity resulted in a recrudescence of pain, inevitably persisting until large doses of narcotics were given. Eventually she began to experience improvement, and was continued on modified bedrest as an outpatient.

Two weeks after discharge she was suddenly seized by excruciating pain which was then located higher in the chest, and radiated to the neck and posterior scapular region on the left. Again the relationship to position and respirations was apparent. As with previous episodes of pain, the electrocardiograms showed generalized T-wave inversion (fig. 3). The "paradoxical pulse," which had been present on the first admission, was not evident. High doses of narcotics, which had not been necessary during her convalescence at home, were again required but afforded only partial relief.

The patient became extremely depressed and emotionally labile, in marked contrast to her cheerful, optimistic personality prior to the illness. In desperation, 15 ml. of 1 per cent Lidocaine were injected about the left stellate ganglion. Within 15 minutes she was completely pain free. A typical Horner's syndrome was observed on the

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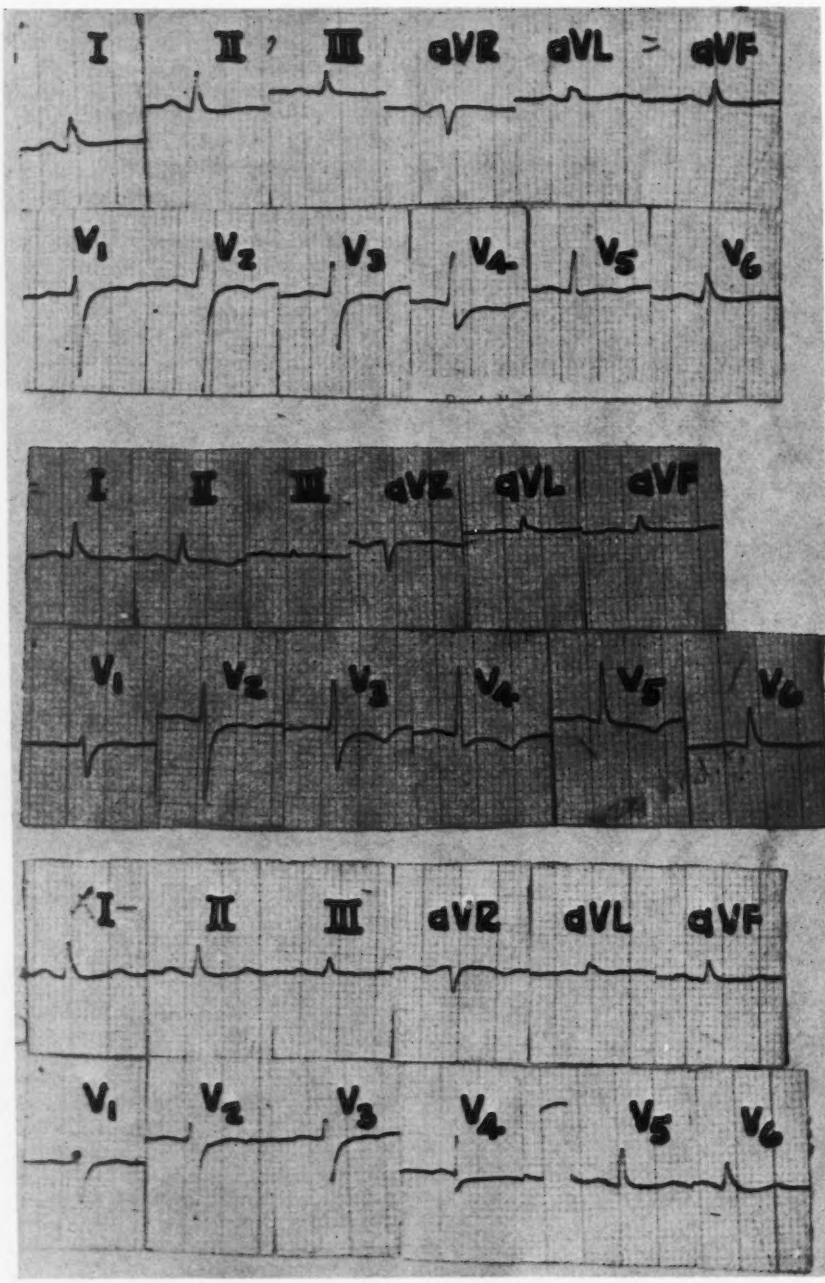


**Figure 1**

Top. *Electrocardiogram, taken 4 hours after admission of patient 1, showing symmetrical inversion of T waves across the precordium.* Middle. *After 8 days of hospitalization; T-wave inversion is more pronounced.* Bottom. *Taken on sixty-fourth day; there is marked improvement, with T-wave inversion manifest only in* $V_2$ *and* $V_3$.

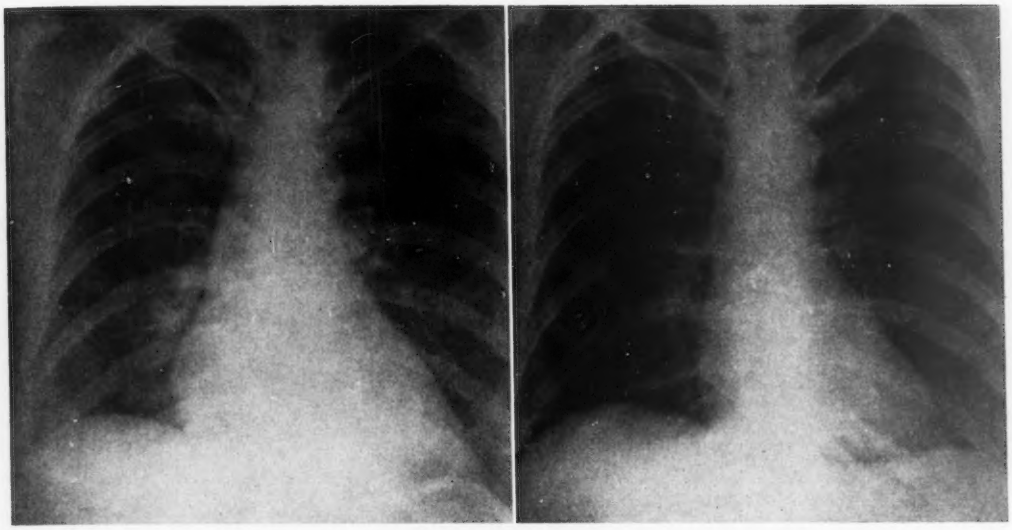

**Figure 2**

Left. *Chest x-ray, taken on the fifth day of hospitalization of patient 1, demonstrates generalized enlargement of the cardiac silhouette, consistent with development of pericardial effusion.* Right. *Complete clearing after 14 days.*

left, as well as increased warmth and flushing of the left upper extremity. To our gratification, she remained asymptomatic for 6 days. Again, however, pain recurred, which was located primarily in the precordial region, and was of only moderate intensity. To test the possible placebo effect of the previous treatment, the stellate block maneuver was repeated, with the injection of 3 ml. of saline solution.

The patient noted some lessening of her discomfort, but this was by no means complete, and the pain recurred the following morning. She continued to require large doses of opiates, and 4 days later, when the pain increased in severity, a third stellate block was performed. On this occasion, as had been done originally, 15 ml. of 1 per cent Lidocaine were administered, and again within 10 minutes the pain was completely relieved.

Following the first and third injections, movements of the left hemidiaphragm were observed under fluoroscopy, establishing that the phrenic nerve had not been inadvertently blocked. The patient has resumed full activity, and has been observed for 3 months without recurrence of pain.

**Case 2**

In October 1960, a 30-year-old soldier awoke with crushing, precordial chest pain that was markedly increased by deep respirations or lying supine. He obtained relief only by sitting up and leaning forward.

The patient was extremely restless and in severe discomfort. The physical examination otherwise was within normal limits except for a "paradoxical pulse" of 15 mm. Hg.

Serial electrocardiograms (fig. 4) showed the typical evolution of acute pericarditis. The cardiac silhouette was not enlarged on x-ray. Serum glutamic pyruvic transaminase was 3 units and serum glutamic oxalacetic transaminase was 2 units. Laboratory tests for other causes of pericarditis were negative.

The patient received narcotics during the first several days of hospitalization with considerable diminution of pain. It was noted, however, that in the evenings he would suffer a severe recrudescence, located primarily in the left side of the neck and left scapular region. Moreover, he stated that he was actually never free of pain. Because of our experience with the first patient, a left stellate ganglion block was performed on the seventh hospital day. Within 10 minutes the patient developed both a Horner's syndrome and erythema and warmth of the left arm. In 30 minutes his pain had completely disappeared. The remainder of his hospital course was uncomplicated, although a friction rub was heard from the tenth to the twenty-fifth day of his hospitalization. He has experienced no

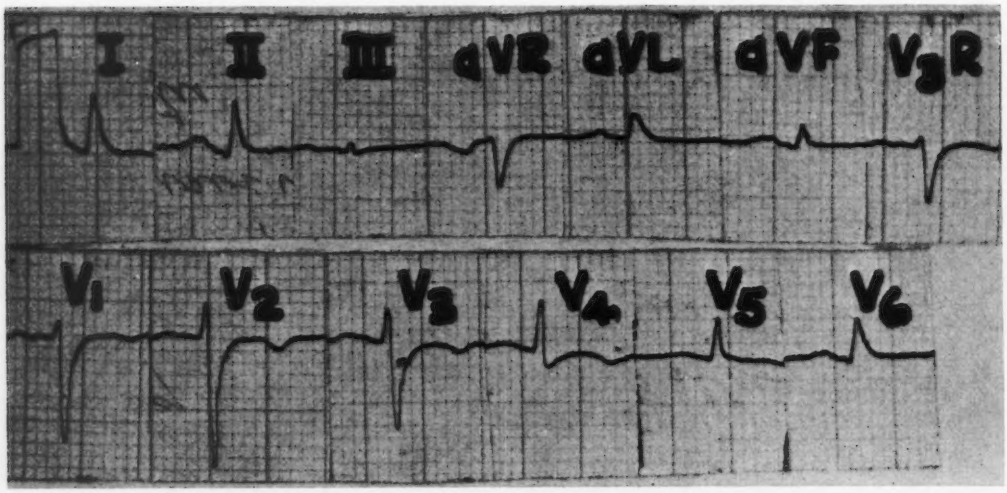


**Figure 3**

*Electrocardiogram taken on patient 1 at the time of second admission. Generalized T-wave inversion has recurred.*

recurrence of pain during a 2-month follow-up period.

## Discussion

The cause of the pain in pericarditis is obscure. In *Gray's Anatomy*[1] it is stated that the nerve supply to the pericardium involves the vagus and phrenic nerves, and also sympathetic trunks. In other basic texts[2-4] afferent fibers from the pericardium are said to be carried through sympathetic and parasympathetic thoracic ganglia. White,[5] and also Bonica,[6] stated that the pericardium is pain-sensitive only on its diaphragmatic aspect, the result of fibers supplied from the left phrenic nerve as it courses toward the diaphragm. They explain the radiation of the pain to the left shoulder and its relation to respiration on this basis. Roberg,[7] while accepting this explanation, believed that the answer may lie in the distortion or compression of mediastinal structures, including the heart itself, by stretching of the pericardium during the inflammatory stage of the disease. Capps et al.[8] believed that the pericardium is insensitive to pain. Carmichael[19] stated frankly that the cause of the recurrent pain in pericarditis is not understood.

Myocardial pain sensitivity, on the other hand, a much more important and prevalent clinical problem, has received a proportionally greater share of attention. Unfortunately, its mechanism is also far from clarified. Herrmann[10] concluded that the autonomic nervous system, including the vagus nerve, superior, middle, and inferior cervical ganglia, the inferior, middle, and superior cardiac nerves, as well as the first through the fifth thoracic ganglia, including the posterior spinal roots, are involved in the mechanism of myocardial pain. He stated that various types of surgical procedures, including the division or resection of all three cervical ganglia, or of the stellate ganglion alone, have resulted in complete and sustained cessation of anginal pain. He makes no mention, however, of the pain pathways of the pericardium.

The stellate ganglion is derived from the last cervical and first thoracic sympathetic ganglia. In both of our patients, the pain was markedly affected by respiration, and was located in the shoulder area. This observation supports the contention of those authors who think that the nerve supply to the pericardium may course along the phrenic nerve. The phrenic is formed from cervical segments three, four, and five, and since both patients

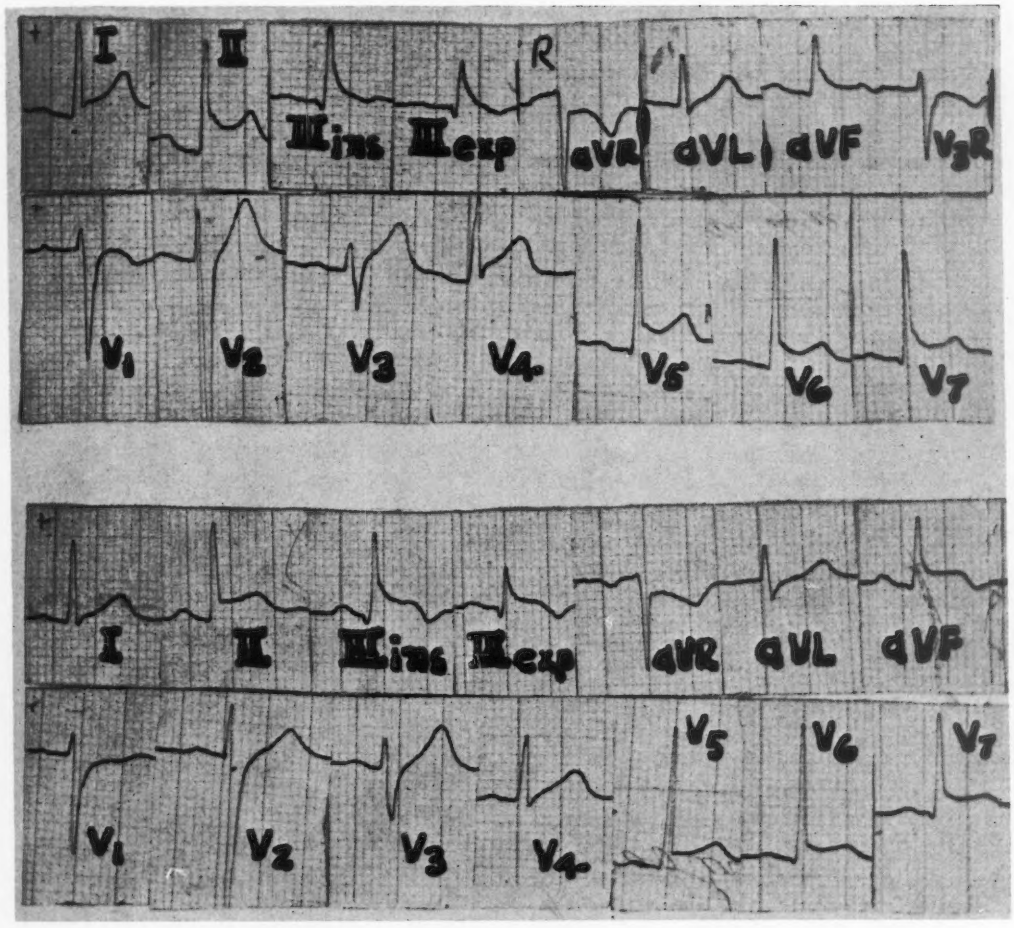


**Figure 4**

Top. *Electrocardiogram taken 6 hours after admission of patient 2. Early S-T elevation is evident in lead II and also in $V_5$ and $V_6$.* Bottom. *Four days after admission. T-wave inversion emerging in leads III and $aV_F$ as S-T segments return toward the baseline.*

experienced complete relief from stellate ganglion block, it seems unlikely that the distribution of the pain is the result of phrenic nerve involvement.

The block was performed as recommended by Moore,[11] who noted many conditions, including angina and "cardiac" pain, for which this procedure is indicated. He stressed that the development of a Horner's syndrome does not necessarily indicate stellate ganglion block, as this syndrome may result from blocking any cervical sympathetic ganglion. Increased warmth, vasodilatation, and increased dryness of the skin of the left arm must be present in addition, as it was in both of our patients.

Our rationale for the employment of this procedure is actually fairly obvious, since it has been used successfully for myocardial pain on many occasions. We planned to follow with a left phrenic block if the stellate block were unsuccessful. It is difficult, of course, to eliminate the nonspecific effect of suggestion, particularly when one injects in such an un-

usual area. The dramatic and complete relief experienced by the patients when Lidocaine was used, as contrasted with the minimal effect of saline, seems good evidence that our objective was truly achieved.

It is realized that most patients with uncomplicated pericarditis do not require therapy of this sort to relieve discomfort. Nevertheless, it might fruitfully be employed in the early stages of the disorder when the pain is severe and, in addition, in the occasional patient who develops incapacitating recurrences. Rehabilitation may be hastened, and severe emotional setbacks minimized.

One might also speculate whether such therapy, if tactfully and reassuringly employed, might not be attempted in the much more common problem of acute myocardial infarction, particularly in those cases that do not respond satisfactorily to narcotics and other traditional methods of therapy.

Because of the source from which our patient material is drawn, primarily young soldiers and their families, we have not had occasion to test the latter hypothesis.

**Summary**

Two patients are presented, in whom dramatic, complete, and prolonged relief from the pain of acute pericarditis was afforded by left stellate ganglion block. In one, this method was successful after the patient had been virtually incapacitated by pain for 75 days. As far as we have been able to ascertain, this mode of therapy has not been previously employed. The distribution of the pain seemed to implicate the phrenic nerve; however, the relief secured by stellate ganglion block appears contrary to this traditional theory.

It is concluded that the mechanism of pericardial pain is not completely understood but that the current, generally accepted explanations are quite likely inaccurate. The inferior cervical and first thoracic sympathetic ganglia may play a large, if not complete role in the transmission of these pain impulses.

There are several practical aspects to our observations. Stellate ganglion block might be logically employed during the acute phase of pericarditis if the pain is severe, and also when the patient is incapacitated by recurrences. There remains also a virtually unexplored field, the relief of the pain of acute myocardial infarction by this procedure.

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# Effect of Anticoagulant Therapy upon Aspirin-Induced Gastrointestinal Bleeding

*By* Richard M. Watson, M.D., and Richard N. Pierson, Jr., M.D.

ASPIRIN has been shown to cause gastrointestinal bleeding. Although the blood loss associated with the relatively small dosage that is customarily used is slight (usually well below 10 ml. per day),[1] there are some situations in which the safety of aspirin may be questioned. Such a situation is the administration of aspirin to patients who are simultaneously receiving anticoagulant therapy. Some authors have, in fact, recommended that such patients should not use salicylates in any form.[2, 3] In view of the increasing number of patients who are receiving anticoagulants on a long-term basis, and the ubiquitous use of aspirin, it is important to know whether significant increase in gastrointestinal blood loss occurs in the presence of this combination of agents. The present study was designed to evaluate the safety of salicylate ingestion in combination with anticoagulation, under controlled conditions. In addition, the possible effect of salicylate ingestion on the dosage of anticoagulant needed to produce satisfactory levels of hypoprothrombinemia was studied.

## Method

The group under study consisted of sixteen men and nine women who were patients on the medical wards of St. Luke's Hospital. These patients, whose ages ranged from 31 to 85, were receiving acenocoumarin* to prevent complications of coronary artery disease, thrombophlebitis, and atrial fibrillation.

Erythrocytes were labeled with sodium radiochromate and reinjected according to a previously described method, and fecal blood content was calculated from the ratio of fecal:blood radioactivity.[4] Prothrombin time was determined by the Link-Shapiro modification of Quick's method.[5] When stable acenocoumarin dosage and prothrombin activity levels were attained, a 3-day quantitative stool specimen was collected and measured for blood content, and the result was considered a control value. Each patient was then given aspirin, 600 mg. four times daily. After a 3-day interval to allow for intestinal transit time, a second stool specimen was similarly obtained and measured. (In a group of 131 normal volunteers, who were previously studied by the same technic, the mean daily control fecal blood content was 0.5 ± 0.4 ml.,† whereas that during periods of aspirin administration of the same dosage, was 4.7 ± 4.1 ml.)

In order to determine the effect of aspirin upon prothrombin activity, the average daily maintenance dosage of acenocoumarin was calculated both before and during the week in which aspirin was given.

## Results

### Fecal Blood Content

Results were obtained for fecal blood loss in 20 patients for control periods, and for 188 patients for aspirin periods. Seventeen patients completed both aspirin and control periods. The observations are summarized in figure 1, in which two groups of subjects are compared: the group receiving anticoagulants during both aspirin and control periods, and a group of 131 normal volunteers who were similarly evaluated during both aspirin and control periods. The average daily blood loss in the anticoagulant group was 1.1 ± 1.0 ml. (range 0.1 to 3.2 ml.) during the control period, and 4.7 ± 3.4 ml. (range 0.8 to 13.0) during the aspirin period. Corresponding figures for the volunteer group were 0.5 ± 0.4 (range 0 to 1.9) and 4.7 ± 4.1 (range 0.5 to 85) ml. respectively. In the volunteer group, 73 per cent of the subjects had a daily fecal blood loss in excess of

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*Sintrom. Geigy Pharmaceuticals, Ardsley, New York.

†S.D. = $\sqrt{\frac{(x - \bar{x})^2}{n - 1}}$

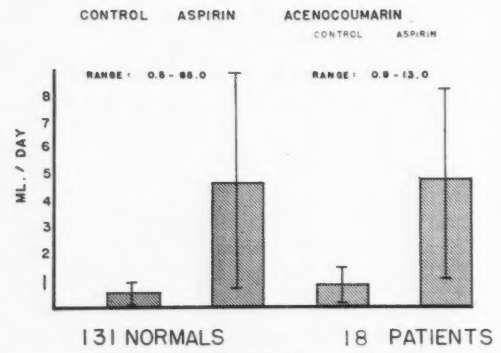


**Figure 1**

*Daily fecal blood loss.*

1.5 ml., or 2½ standard deviations above their own mean control level during aspirin period. Of the subjects receiving the anticoagulant, 76 per cent showed a daily blood loss in excess of 1.5 ml. during the aspirin periods. Since the control level of the latter group is higher, however, the establishment of an acceptable "significant" increase in rate of bleeding is correspondingly higher. Thus, 67 per cent of the subjects receiving anticoagulants had a daily blood loss during the aspirin period that was 2½ standard deviations, or more, above their own control level.

**Alterations in Anticoagulant Dosage**

Seventeen patients were observed for a sufficient length of time both with and without aspirin to calculate average daily maintenance dosages of acenocoumarin (fig. 2). Eleven of these patients required a reduction in daily acenocoumarin dosage of 0.5 mg. or more. These patients were maintained on a daily average of 3.1 mg. of acenocoumarin during the control period and 2.2 mg. during the aspirin period. Five other patients required a dosage reduction of less than 0.5 mg.; this was not considered significant because of the inaccuracy of dividing the 4-mg. tablet. Only one patient had an increase in maintenance dosage while taking aspirin, and this increment was only 0.5 mg. The daily blood loss in those patients in whom aspirin seemed to have a hypoprothrombinemic effect was no greater than in the others. Thus, there was no correlation between bleeding tendency and aspirin-induced hypoprothrombinemia.

**Complications**

Anticoagulant therapy had to be discontinued in four patients during the course of the study. One of the patients experienced frequent episodes of epistaxis while taking aspirin, but he had previously shown an elevation in fecal blood content (7.2 ml. per day) during the control period. Another patient had a sudden episode of rectal bleeding during which 140 ml. of blood were lost; the source of this bleeding was believed to be hemorrhoidal. A third patient developed gross hematuria before aspirin was started. The fourth had an episode of upper gastrointestinal bleeding, also before aspirin was started. Thus, aspirin could not be incriminated in any of these complications. These patients are not included in table 1.

## Discussion

A variety of mechanisms have been proposed in order to explain the bleeding that occurs with the ingestion of aspirin:

1. *Hypoprothrombinemia.* Link and coworkers[6] first showed that salicylic acid could produce hypoprothrombinemia in rats, and actually postulated that degradation to salicylic acid was the basis of the prothrombin-depressing effect of bishydroxycoumarin. More recently, evidence has been produced to challenge the latter point.[2, 7]

Rapoport et al.,[8] Meyer and Howard,[9] and Shapiro et al.[10] subsequently described a similar hypoprothrombinemic effect, both with aspirin and sodium salicylate, upon human beings. Although clinical reports have ascribed hematemesis following aspirin use to hypoprothrombinemia,[11, 12] the prothrombin levels quoted are not sufficiently low to explain such bleeding. The present study suggests that hypoprothrombinemia is not a significant factor in salicylate bleeding.

2. *Gastritis.* Douthwaite and Lintott[13] have reported gastroscopic observations on subjects who had previously swallowed aspirin tablets, and described a generalized gastritis, in

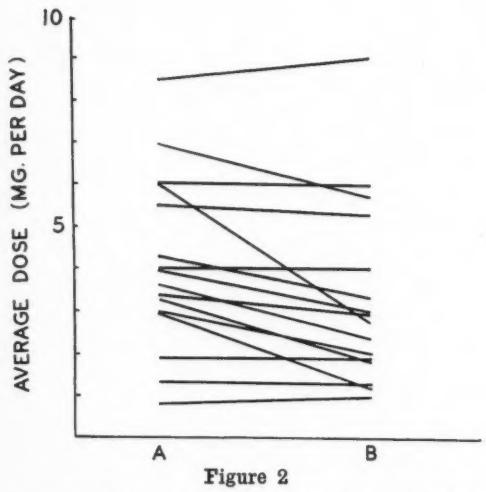


**Figure 2**

*Acenocoumarin requirements during control (A) and aspirin (B) periods.*

addition to small areas of hyperemia surrounding undissolved particles of aspirin. They also reported submucous hemorrhages, as well as actual bleeding points. Muir and Cossar[14] examined the stomachs of patients who had received aspirin prior to gastrectomy, and described similar changes, with the additional finding of minute ulcerations beneath the undissolved particles.

3. *Exacerbation of peptic ulceration.* There have been reports[14-16] of both ulcer symptoms and of gastrointestinal bleeding appearing after aspirin ingestion. The manner in which aspirin might activate peptic disease is not clear, but it has been suggested that this may be due to the action of an irritant upon the chronic gastritis that frequently exists in the individual with peptic disease.[14] Of particular interest in these reports is the tendency toward repetition of gastric complications (both ulcer symptoms and bleeding) following the use of aspirin by such individuals.

4. *Capillary fragility.* This has been described as a factor in the bleeding of salicylate toxicity because of the appearance of a positive Rumpel-Leeds test in the presence of an otherwise intact clotting mechanism (other than mild hypoprothrombinemia).[17] This has also been shown in a pathologic study of two patients who died of hemorrhagic complications following heavy doses of salicylates, in whom numerous microscopic petechiae were found.[11]

5. *Thrombocytopenic purpura.* Although this has been reported to occur following the use of aspirin, it is very rare.[18]

The relevant effects that have been most consistently observed with small analgesic

**Table 1**

*Summary of Patients and Results*

| Patient | Sex and age | Diagnosis | Blood loss ml./Day | Average daily dose acenocoumarin (mg.) |
|---|---|---|---|---|
| 1 AP | M 50 | MI | C 2.6 | 3.4 |
| | | | A 13.0 | 2.9 |
| 2 IR | M 62 | MI | C 0 | 4.0 |
| | | | A 2.2 | 3.0 |
| 3 EG | M 57 | MI | C 0.4 | 8.5 |
| | | | A 1.3 | 9.0 |
| 4 MQ | F 75 | MI | C 2.0 | 3.6 |
| | | | A 5.6 | 2.4 |
| 5 AG | M 76 | MI | C 0.2 | 3.0 |
| | | | A 3.4 | 1.2 |
| 6 JC | F 70 | MI | C 0.8 | 0.9 |
| | | | A 1.3 | 1.0 |
| 7 DU | M 31 | RHD, AF | C 0.9 | 3.4 |
| | | | A 5.8 | 2.9 |
| 8 JC | M 45 | Angina | C 0.1 | 1.4 |
| | | | A 0.8 | 1.3 |
| 9 CG | F 50 | RHD, AF | C 0.2 | 4.3 |
| | | | A 8.4 | 3.8 |
| 10 ML | M 78 | MI | C — | 4.0 |
| | | | A 3.2 | 4.0 |
| 11 TC | M 59 | MI | C 3.2 | 3.3 |
| | | | A 1.4 | 1.8 |
| 12 AM | M 69 | AF | C 1.5 | 5.5 |
| | | | A 7.4 | 5.3 |
| 13 PM | M 56 | MI | C 0.3 | 1.9 |
| | | | A 2.0 | 1.9 |
| 14 AG | M 43 | MI | C 0.7 | 3.0 |
| | | | A 7.2 | 2.0 |
| 15 JM | F 46 | MI | C 0.3 | 6.0 |
| | | | A — | 6.0 |
| 16 IB | F 51 | MI | C 2.6 | 7.0 |
| | | | A — | 5.7 |
| 17 JA | F 68 | MI | C 2.8 | 6.0 |
| | | | A — | 2.8 |
| 18 CM | F 35 | Thr. | C 1.5 | — |
| | | | A 7.6 | — |
| 19 JS | M 43 | MI | C 6.0 | — |
| | | | A 5.3 | — |
| 20 CS | M 47 | MI | C 0 | — |
| | | | A 3.2 | — |
| 21 MS | M 41 | Angina | C .2 | — |
| | | | A 9.6 | — |

AF, atrial fibrillation; MI, myocardial infarction; RHD, rheumatic heart disease; Thr., thrombophlebitis; C, control period; A, aspirin period.

doses of aspirin are those of gastritis[13, 14] and a lowered prothrombin activity.[11] In the present study, and in a previous study of normal volunteers,[19] lowered prothrombin activity was not correlated with daily blood loss. The results suggest, however, that an already low prothrombin level might, in an occasional patient, be further depressed to a dangerous level. Such an incident was not observed in this group of patients because prothrombin determinations were performed every day, and appropriate dose adjustments were made. Since the rate of bleeding did not appear to be influenced by anticoagulation, it would be tempting to deny any hazard in the use of aspirin. More extensive bleeding has been observed, however, in 5 to 10 per cent of normal volunteers studied in this laboratory (up to 85 ml. per day). Since no such persons were found in this study group, it is impossible to predict the influence of anticoagulation upon "susceptible" persons with aspirin-induced bleeding of this magnitude.

### Summary and Conclusions

A group of patients receiving oral anticoagulants was studied during control periods and periods during which aspirin was administered, with respect to rate of blood loss via the gastrointestinal tract. These patients did not bleed at a significantly greater rate than did previously studied normal volunteers, when taking aspirin; however, the anticoagulant group showed a slightly higher blood loss during the control period.

The majority of patients showed a slight though detectable decrease in prothrombin activity, as evidenced by a reduction in anticoagulant dosage, during the aspirin period.

The results of this study indicate that aspirin, in a dose of 600 mg. four times daily, rendered no apparent increased hazard of gastrointestinal bleeding in the small group of subjects without evident gastrointestinal disease studied. Patients who must take aspirin continuously, however, may require a reduction in anticoagulant maintenance dosage.

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# A Comparison of the Pulmonary Blood Flow between Left and Right Lungs in Normal Subjects and Patients with Congenital Heart Disease

*By* C. T. Dollery, M.B., J. B. West, M.D., D. E. L. Wilcken, M.B., and P. Hugh-Jones, M.D.

CARBON DIOXIDE labeled with oxygen-15 can be used to compare the blood flow in different regions of the lung. The subject takes a quick breath of a known volume of air containing a minute proportion of labeled carbon dioxide and then he holds his breath for about 10 seconds. The gamma rays emitted by the isotope penetrate the chest wall and can be detected by pairs of crystal scintillation counters arranged opposite each other, front and back, over the chest. The rate of fall of counting rate during the period of apnea is used as a measure of the regional blood flow through the cylinder of lung tissue between the counters.

Various factors, including posture, exercise, total pulmonary blood flow, and changes in pulmonary artery and venous pressures, influence the regional partition of blood flow through the lungs. Normal subjects sitting upright at rest have a low flow at the apex of the lung and a progressive increase toward the base; when they lie flat, the flow in the two regions becomes equal.[1] When normal subjects sitting upright do leg exercise, the flow increases at both apex and base but the difference between the two becomes less.[1] Patients with cardiac shunts and high pulmonary blood flow have a regional perfusion similar to normal subjects on exercise. Patients with cardiac shunts and pulmonary hypertension have equal flow at the apex and base of the lung.[2] All these results can be explained by supposing that hydrostatic pressure due to gravity influences the regional blood flow in the resting normal subject and that this factor is less important when the total pulmonary flow or the pulmonary artery pressure is high. Patients with very severe mitral stenosis have a higher blood flow through the apical regions of the lung than the basal, and it is possible that this change is related to the rise in pulmonary venous pressure in this disease.[3]

Patients with obstruction of the pulmonary outflow tract present another opportunity for assessing the effect of hydrostatic pressure, for they often have a low pulmonary artery pressure and low pulmonary blood flow. During a study of a group of patients with this condition we found unequal flow through the left and right upper zones, so comparisons of flow in the upper zones were made in normal subjects and in patients with atrial septal defects, ventricular septal defects, and patent ductus arteriosus.

## Methods

### Production of the Radioactive Carbon Dioxide

The method was that used in previous investigations. Oxygen-15, which has a half life of 2 minutes, was produced by deuteron bombardment of nitrogen in the Medical Research Council cyclotron at Hammersmith Hospital. The target gas consisted of pure nitrogen with 4 per cent of oxygen to act as carrier for the oxygen-15. This gas mixture flowed continuously through the target box during the investigations. The labeled gas was piped to the chemical laboratory, where it was first passed over hot charcoal at 450 C. and then over copper oxide at 900 C. The charcoal converted most of the oxygen to carbon dioxide, and the small amount of carbon monoxide formed was converted to carbon dioxide by the copper oxide. The completion of chemical conversion was checked by analyzing the exit gases from the fur-

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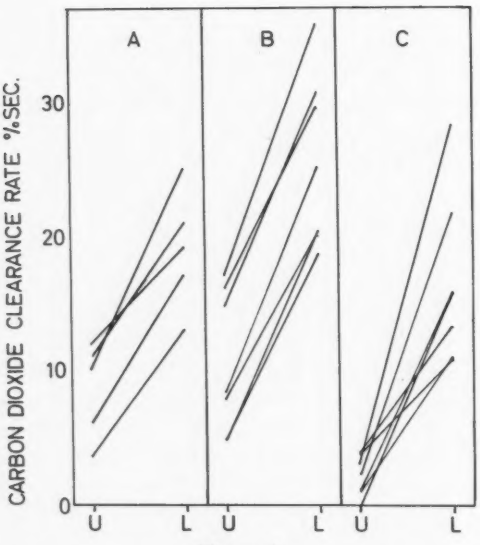


**Figure 1**

*The clearance rates of radioactive carbon dioxide at the left second rib (U) and 4 inches (10 cm.) lower on the right side (L). Each line connects the upper and lower zone clearance rates of an individual patient. Section A shows results in five normal subjects; section B, seven patients with isolated pulmonary stenosis; and section C, seven patients with the tetralogy of Fallot.*

naces for carbon monoxide with an infrared meter and for oxygen with a mass spectrometer. The purity of the radioactive constituents was checked by plotting the radioactive decay curve.

The gas from the furnaces was diluted with a stream of air and the radioactivity was monitored continuously by passing the diluted gas through a glass bulb in a re-entrant ionization chamber.

**Procedure**

The patient sat upright in a chair with pairs of crystal scintillation counters arranged in front of and behind each lung. Each pair of counters could be moved hydraulically so that its height could be regulated independently. In this investigation parallel counting was used in which the outputs from the pair of counters on one side were added together electronically, passed through rate meters, and displayed on pen recorders. Each pen recorder therefore showed the total counts contributed from the cylindrical counting field in one lung. The counters were accurately aligned so that the counting field was a cylinder of lung tissue, about 9 cm. in diameter, between the pair of crystals.

The patient breathed through a respiratory valve box with a low deadspace, and at the end of a normal expiration took a rapid inspiration from a plastic bag containing 900 ml. of air containing a small quantity of carbon dioxide of which a minute proportion was labeled with oxygen-15. As soon as the bag was empty, the patient held his breath for about 10 seconds and then resumed normal breathing.

**Analysis of Records**

The records show a rapid increase in counting rate as the patient breathes in and draws the radioactive gas into the lung within the counting field (figs. 2 and 3). During the period of apnea the counting rate falls exponentially for the first few seconds, until recirculation takes place. The curves were plotted on a semilogarithmic scale after allowance for background radiation and radioactive decay. The slope of the semilogarithmic plot was then expressed as the carbon dioxide clearance rate in per cent per second of the instantaneous activity.

Carbon dioxide labeled with oxygen-15 is removed from the alveoli extremely rapidly because carbon dioxide is very diffusible, and the exchange of the oxygen-15 from bicarbonate ions wtih hydroxyl ions in water ensures that there is no significant back pressure.[4] The curves therefore record the rate of removal of the labeled pulmonary capillary blood from the counting field; this has been used as a measure of regional blood flow.

**Normal Values**

With the use of this technic values of carbon dioxide clearance rate in different regions of the lung were obtained from some normal subjects. In an earlier investigation measurements were made in normal subjects in a basal state, at the level of the left second rib, and 10 cm. lower over the right lung. The mean clearance rate at the second rib was 4.8 per cent per second (S.E. 2.1) and 10 cm. lower 25.9 per cent per second (S.E. 1.7).

During the present study a total of 20 paired observations of the upper zone clearance rate was made in six young normal members of the hospital staff. The mean left upper zone clearance rate was 12.2 per cent per second (S.D. 5.9) and the mean right upper zone clearance rate 10.5 per cent per second (S.D. 4.7). The difference between the left and right upper zone clearance rates of each individual divided by the mean of the left and right upper zone clearance rates of that individual was used for statistical analysis. The difference between the individual paired values of left and right upper zone clearance rates was significant ($p < 0.001$), despite the small separation of the group means for the left and right sides because

**Table 1**

*Hemodynamic Data and Rates of Clearance of Carbon Dioxide*

| Diagnosis | Case no. | Age (yr.) | Pressures mm. Hg | | Arterial saturation (%) | Carbon dioxide clearance rate % per second | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | Right ventricle | Pulmonary artery | | Left upper zone | Right upper zone | Left upper zone | Right lower zone |
| | | | | | | Measured simultaneously | | Measured simultaneously | |
| A | 1 | 14 | 47/0 | 21/8 | 94 | 13.9 | 11.0 | 4.9 | 20.4 |
| Pulmonary | 2 | 10 | 65/0 | 21/10 | 93 | 9.5 | 10.4 | 14.8 | 30.9 |
| stenosis | 3 | 8 | 80/0 | 31/18 | 94 | 25.1 | 5.7 | 17.2 | 35.9 |
| | 4 | 14 | 90/5 | 10/5 | 96 | — | — | 16.3 | 29.6 |
| | 5 | 16 | 110/30 | 15/5 | 94 | 7.8 | 2.1 | 8.4 | 25.1 |
| | 6 | 20 | 112/0 | — | 94 | 4.0 | 2.5 | 4.8 | 18.7 |
| | 7 | 13 | 130/7 | 15/10 | 96 | 5.0 | 2.3 | 7.9 | 20.4 |
| B | 8 | 44 | 119/0 | 12/0 | 90 | 0.2 | 0 | 1.2 | 15.9 |
| Tetralogy | 9 | 12 | 78/0 | 4/0 | 85 | 10.6 | 7.1 | 1.0 | 11.0 |
| of Fallot | 10 | 12 | 115/0 | 14/0 | 84 | 0 | 0 | 0 | 15.9 |
| | 11 | 13 | 120/2 | 7/0 | 84 | 3.8 | 1.1 | 3.8 | 10.8 |
| | 12 | 10 | 90/0 | — | — | 0 | 0 | 2.3 | 21.8 |
| | 13 | 10 | 120/0 | — | 79 | 5.2 | 3.1 | 3.1 | 28.3 |
| | 14 | 15 | 104/0 | 9/2 | 74 | 6.6 | 0.3 | 3.9 | 13.3 |

**Table 2**

*Atrial Septal Defect*

| Case no. | Age (yr.) | Pulmonary to systemic flow ratios | Pulmonary artery pressure (mm. Hg) | Total resistance units | $CO_2$ clearances %/second | |
|---|---|---|---|---|---|---|
| | | | | | Left upper zone | Right upper zone |
| 15 | 50 | 2:1 | 29/9 | 1 | 16 | 17 |
| 16 | 7 | 1.9:1 | 15/8 | 2 | 29 | 32 |
| 17 | 13 | 3:1 | 28/4 | 1 | 26 | 32 |
| 18 | 36 | 1.7:1 | 45/0 (RV) | — | 30 | 28 |
| 19 | 18 | 3.5:1 | 28/9 | 1 | 40 | 38 |
| 20 | 44 | 2.4:1 | 34/14 | 3 | 32 | 34 |
| 21 | 19 | 2.8:1 | 35/10 | 3 | 32 | 29 |
| 22 | 34 | 2:1 | 74/32 | 5 | 11 | 28 |
| 23 | 13 | 2:1 | 10/5 | 1 | 40 | 30 |
| 24 | 33 | 3.5:1 | 40/10 | 1 | 28 | 44 |

the difference was consistent. The values of upper zone clearance obtained in this study were higher than the previous normal values but on this occasion no special precautions were taken to ensure that the normal subjects were in a basal state. The upper zone values are very sensitive to anxiety and exercise.

**Patients with Pulmonary Stenosis**

Fourteen patients with obstruction of right ventricular outflow tract and reduced pulmonary artery pressure and flow were studied. There were seven with lone pulmonary stenosis (five valvular, two infundibular) and seven with the tetralogy of Fallot. The diagnoses were made on clinical evidence including electrocardiography and radiography, and verified in all cases by routine right heart catheterization. In the seven patients with the tetralogy of Fallot angiocardiography provided additional confirmation of the diagnosis.

Relevant hemodynamic data are listed in table 1. Of the patients who had only pulmonary stenosis two were mild, having pressure gradients of 26 and 44 mm. Hg across the valve (cases 1 and 2); two were moderately severe with gradients of 80 and 90 mm. Hg (cases 3 and 4); and three more severe with gradients of over 100 mm. Hg (cases 5, 6, and 7). The arterial saturation was normal in all these patients, and none gave a history of cyanosis on effort. In the patients with the tetralogy of Fallot the resting arterial oxygen saturation was regarded as an index of severity of the

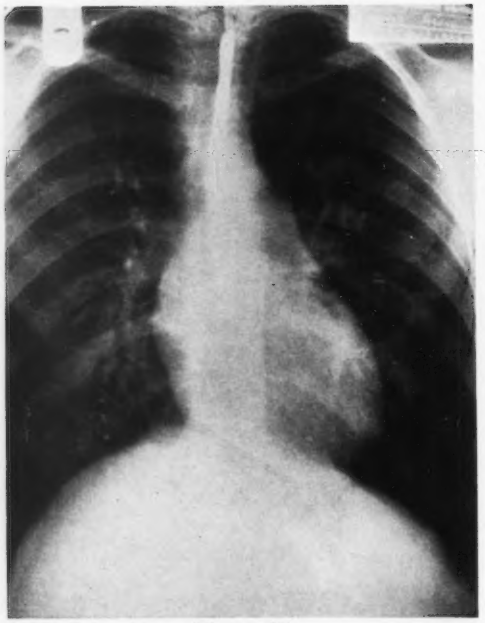

**Figure 2A**

*The chest x-ray of a patient (case 7) with isolated pulmonary stenosis, to show the oligemic lungs.*

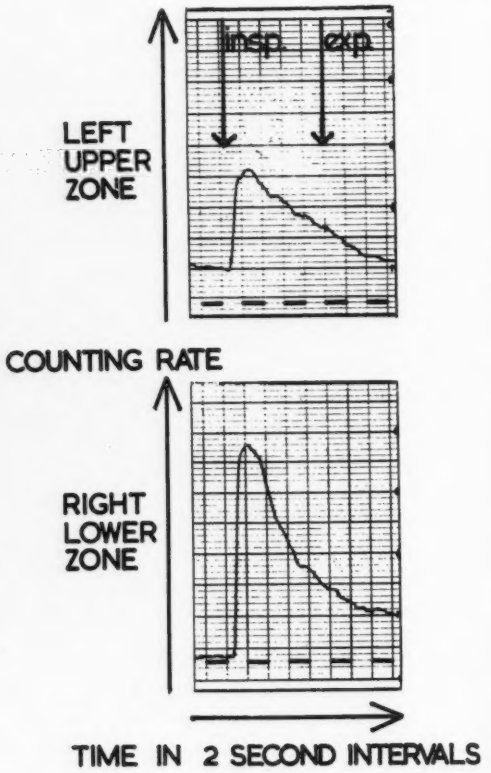


**Figure 2B**

*The carbon dioxide clearance curves from the upper and lower zones had a normal slope, 7.9 per cent per second and 20.4 per cent per second.*

outflow tract obstruction. This varied between 91 per cent and 74 per cent.

### Patients with Left-to-Right Shunts

A group of patients with left-to-right shunts was also studied and the findings were compared with the data obtained from patients with pulmonary outflow tract obstruction. There were 10 patients with atrial septal defect, eight with ventricular septal defect, and four with patent ductus arteriosus. In all but two patients with patent ductus arteriosus the diagnosis was confirmed by cardiac catheterization. All the patients with ventricular septal defects and the majority with atrial septal defects were studied by angiocardiography. Hemodynamic data on the patients with atrial septal defects are in table 2.

## Results

### Pulmonary Stenosis and Tetralogy of Fallot

The hemodynamic data and the carbon dioxide clearance rates of the patients with pulmonary stenosis have been brought together in table 1. The patients fall naturally into two groups, those with pulmonary stenosis and those with Fallot's tetralogy.

The clearance rates in patients with isolated pulmonary stenosis were not significantly different from normal values in any zone. The mean clearance rate from the two upper zones was 8.3 per cent per second (S.D. 6.5) and the mean from the two upper zones in normal subjects was 11.4 per cent per second (S.D. 5.3). Three patients (cases 2, 3, and 4) had high clearance rates from both zones that are unexplained. The mean clearance rate from the right lower zone was 25.9 per cent per second (S.D. 6.5) and the normal value was 23.5 per cent per second (S.D. 1.7). Clearance rate measurements from the left upper zone appear twice in table 1 and the values often differ. The lower values were obtained later in the recording session and it is thought that this is an effect of rest with reduction in cardiac output. To minimize the effects of this kind of varia-

tion the order of regional measurements was randomized. Despite these changes the ratio of clearance rates in the two upper zones maintained a similar relationship throughout the time of measurement.

Patients with the tetralogy of Fallot had lower carbon dioxide clearance rates than normal subjects in both upper and lower zones. The mean upper zone clearance rate was 2.1 (S.D. 1.7) and the mean lower zone clearance rate was 16.7 per cent per second (S.D. 6.3). These results are in accord with the low pulmonary blood flow associated with the right-to-left cardiac shunt in this disease.

The upper and lower zone comparisons for individual patients are shown graphically in figure 1. Measurements were also made at a level 5 cm. below the second rib in three patients with Fallot's tetralogy in whom the upper zone clearance rates were zero. These results are shown in table 3.

An interesting point arose when comparisons were made of the carbon dioxide clearance rates from the two upper zones in both pulmonary stenosis and the tetralogy of Fallot. There was a significant difference ($p < 0.01$) between the individual paired clearance rates, the left side showing the faster clearance. Normal subjects also had a higher clearance rate at the left upper zone (12.2 per cent per second) than the right (10.5 per cent per second) and the difference between the individual paired values was significant ($p < 0.001$). The preponderance of flow through the left upper zone in normal subjects was proportionately less than in patients with pulmonary stenosis and the tetralogy of Fallot, the difference between the groups being highly significant ($p < 0.001$). The results are illustrated by the following two case reports.

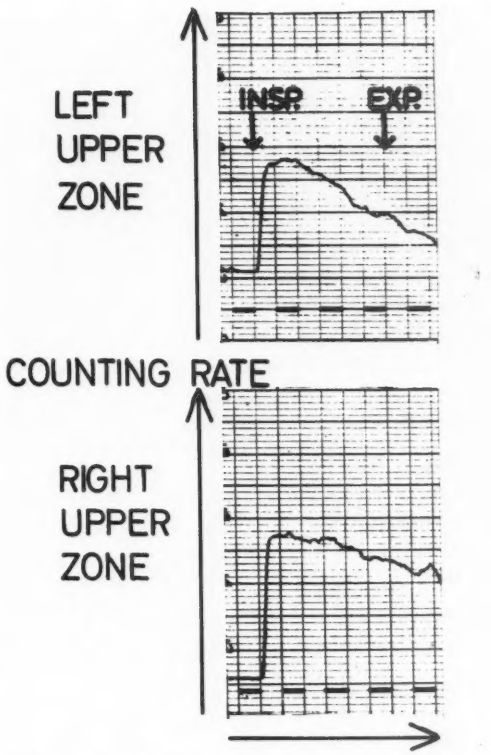


**Figure 2C**

*The clearance rate from the left upper zone (5.0 per cent per second) was twice that from the right upper zone (2.3 per cent per second). The patient inhaled the gas at the first arrow and exhaled at the second; the dotted line is the baseline.*

### Case Reports

#### Case 7

The patient was a boy aged 13. Pulmonary stenosis had been diagnosed at the age of 5, but he had been asymptomatic until recently when his parents noticed that he was tiring more easily during exertion. He continued to take part in all school activities. There was no history of cyanosis or chest pain.

The jugular venous pulse showed an "a" wave 5 cm. above the sternal angle. There were a strong left parasternal lift over the right ventricle and a long systolic thrill and murmur maximal in the second left intercostal space. The pulmonary element of the second sound was soft and delayed and occurred 0.08 second after the aortic element. On the electrocardiogram there was a tall R wave and no "S" wave in lead $V_1$ with inverted T waves extending across to lead $V_3$. Cardiac catheterization confirmed the diagnosis. A systolic pressure gradient of 115 mm. Hg was found at valve level: the pulmonary artery pressure was 15/10 mm. Hg. The arterial saturation was normal and no shunts were detected. Radioactive carbon dioxide clearance curves and the chest x-ray are shown in figure 2. The chest radiograph shows oligemia of the lung

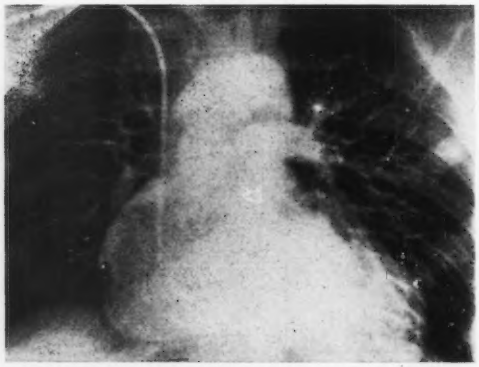

**Figure 3A**

*The angiocardiogram of a patient (case 14) with Fallot's tetralogy, showing simultaneous filling of the aorta and pulmonary artery. The filling of the pulmonary arteries in the lung fields is greater on the left than on the right.*

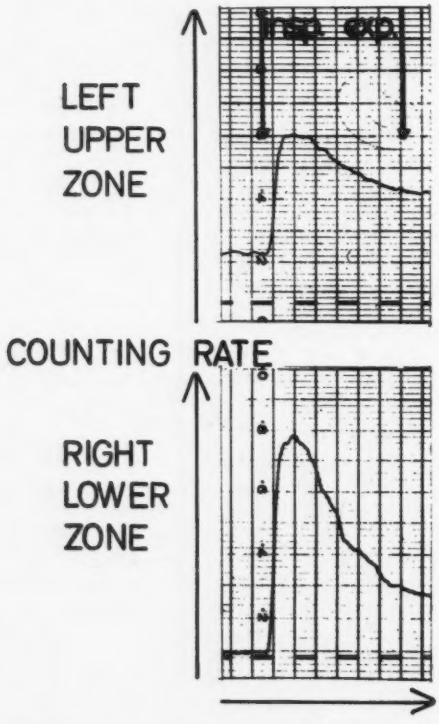


**Figure 3B**

*The carbon dioxide clearance rate was 3.9 per cent per second from the upper zone and 13.3 per cent per second from the lower zone; both values are low.*

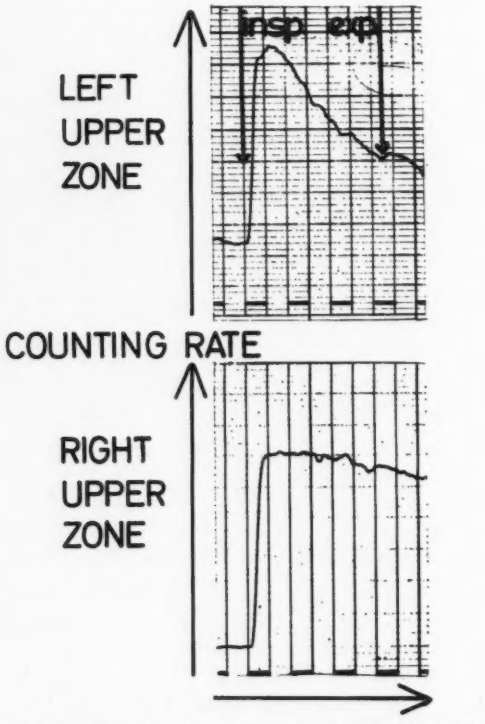


**Figure 3C**

*Comparison of the two upper zones showed a clearance rate of 6.6 per cent per second on the left and only 0.3 per cent per second on the right.*

fields. The carbon dioxide clearance rate was 7.9 per cent per second at the level of the left second rib and 20.4 per cent per second 4 inches (10 cm.) lower on the right. Simultaneous measurements at the level of the second rib on both sides showed a clearance rate of 5.0 per cent per second on the left and 2.7 per cent per second on the right.

**Case 14**

The patient, a boy of 15, had the tetralogy of Fallot. He was first noticed to be blue at the age of 3. There was no history of syncopal attacks but he used frequently to squat when breathless. He had dyspnea when climbing stairs or walking rapidly on a flat surface.

There was central cyanosis at rest. He was polycythemic, and the fingers and toes were clubbed. The venous and arterial pulses were normal. The cardiac impulse was right ventricular in type and there was a long ejection-type systolic murmur maximal over the left second interspace. No thrill was felt, and on auscultation the second sound was

single. The electrocardiogram showed right ventricular hypertrophy. The pressure gradient between the body of the right ventricle and the pulmonary artery at cardiac catheterization was 95 mm. Hg. There was obstruction at both valve and infundibular levels. The pulmonary artery pressure was 9/2 mm. Hg and the resting arterial saturation was 74 per cent. Selective angiography demonstrated early filling of the aorta and confirmed that the obstruction was mainly valvular (fig. 3*A*). The carbon dioxide results show that the clearance rate at the left second rib was 3.9 per cent per second, and 4 inches (10 cm.) lower on the right it was 13.3 per cent per second (fig. 3*B*). Simultaneous measurements in the two upper zones (fig. 3*C*) showed a clearance rate of 6.6 per cent per second on the left and 0.3 per cent per second on the right.

**Atrial Septal Defect**

There were 10 patients with this diagnosis. The hemodynamic data and the measurements of carbon dioxide clearance rate have been summarized in table 2. The measured carbon dioxide clearance rates were high, in keeping with the high pulmonary blood flow. The relevance of these results to the present paper concerns the comparison of the two upper zones. The mean left upper zone clearance rate was 28.4 per cent per second (S.D. 9.2) and the right upper zone 31.1 per cent per second (S.D. 7.1). The difference between the upper zones was small but that between the individual paired values was significant ($p < 0.02$). Normal subjects have a slightly higher flow through the left upper zone than the right in contrast to patients with atrial septal defects who had the higher flow on the right side: a significant difference ($p < 0.01$) between the groups.

**Ventricular Septal Defect and Patent Ductus Arteriosus**

There were eight patients with ventricular septal defects. The mean left upper zone clearance rate was 32.6 per cent per second (S.D. 9.0) and the right upper zone 32.2 per cent per second (S.D. 9.6). There was no significant difference between the individual paired upper zone clearance rates in this group. There were only four patients with patent ductus arteriosus. The paired upper zone clearance rates in these four patients were closely similar.

**Table 3**

*Clearance Rates 5 cm. Below the Level of the Second Rib in Three Patients with Fallot's Tetralogy Who Had No Clearance at the Second Rib*

| Patient | Clearance rate 5 cm. below second rib %/second | |
|---|---|---|
| | Left | Right |
| 8 | — | 3.5 |
| 10 | 1.7 | 1.1 |
| 12 | 3.8 | 2.6 |

**Discussion**

The carbon dioxide clearance rates have been used as a measure of regional blood flow in this study. Several factors probably affect the clearance rate of the labeled pulmonary capillary blood from the counting field. These include the volume flow rate, the degree of mixing, and the pulmonary venous and capillary blood volumes in the counting field. Since the clearance curves are affected by all these factors, they can most safely be used to compare blood flow through different regions of the lung of the same patient, or, as in the present investigation, to compare the blood flow through similar areas of a patient's left and right lung. The regional clearance rates of the upper zones are particularly sensitive to excitement, presumably because of changes in cardiac output.

The observed differences between the flow in the left and right upper zones in patients with pulmonary stenosis, atrial septal defects, and normal subjects were usually only moderate but they were consistent. The most striking finding was the preponderance of blood flow through the left upper zone in some patients with pulmonary stenosis, both with and without a closed ventricular septum. It was surprising to find that normal subjects also showed a higher flow in the left upper zone than the right, although the difference between the two zones was proportionately smaller than in the patients with pulmonary stenosis. A similar difference appeared in previous measurements on normal subjects[1] but numbers were small. By contrast patients with atrial septal defects showed a small but significant preponderance of flow through the

right upper zone. The patients with ventricular septal defect and patent ductus arteriosus had almost identical flows through the two upper zones.

The difference in clearance between left and right upper zones in normal subjects may be because the main pulmonary artery is directed toward the left lung, and the momentum of the blood partly determines its distribution. If this is a factor, the difference between the two lungs should be more marked when the velocity of the blood ejected into the pulmonary artery is higher, and the greater left-to-right difference found in patients with pulmonary stenosis supports this suggestion. In pulmonary stenosis the blood moves through the narrow valve as a fast jet.

The higher right upper zone clearance rates in patients with atrial septal defects are consistent with the findings of Fleming,[5] who found a much higher oxygen uptake in the right lung than the left, by bronchospirometry. If the heart is enlarged, radioactive blood in it may interfere with clearance curves recorded from the left lower zone; so it is unwise to compare the flow through the two lower zones by our method. It is therefore impractical to determine whether or not a preponderance of flow through one apex reflects a similar situation throughout the whole lung.

The patients with isolated pulmonary stenosis had relatively normal flow rates in both the upper and lower zones, but the patients with the tetralogy of Fallot had low values in both zones. This presumably reflects the low total pulmonary blood flow in these patients. Three patients with the tetralogy of Fallot who had no clearance at the level of the second rib had low clearance rates 5 cm. lower. These patients had oligemia of the upper one third of the lung.

In 1946 Dock,[6] using the data of Cournand and his co-workers,[7] calculated that the effective pulmonary artery pressure near the lung apices in an erect man would be close to zero. He suggested that this explained the apical localization of pulmonary tuberculosis, and that the higher incidence of the disease at the right apex than the left might be the result of higher blood flow at the left apex as the blood gushed from the conus straight into the left pulmonary artery. Dock pointed out that patients with pulmonary stenosis, particularly those with the tetralogy of Fallot, have a high incidence of apical pulmonary tuberculosis. It is interesting that the predictions that Dock made about the apical pulmonary blood flow, from the localization of pulmonary tuberculosis in patients with a normal cardiovascular system, are exactly those found experimentally in this study.

**Summary**

Carbon dioxide labeled with oxygen-15 has been used to study the regional blood flow in the lungs of patients with pulmonary stenosis. The upper and lower zone flows were normal in patients with isolated pulmonary stenosis, but both were low in patients with the tetralogy of Fallot. A comparison of the two upper zones showed a significantly higher blood flow through the left upper zone in patients with both isolated pulmonary stenosis and the tetralogy of Fallot.

A significantly higher flow was also found through the left upper zone than the right of normal subjects. By contrast, patients with atrial septal defect had a higher flow through the right upper zone than the left. Neither difference was as large as in the patients with right ventricular outflow tract obstruction.

Patients with ventricular septal defect and those with patent ductus arteriosus had almost identical flow through the two upper zones.

**Acknowledgment**

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There is certain evidence in the history of research for the belief that some discoveries could not have been made until some other discovery had been made. This fact underlies an aspect of research that has nothing to do with our roulette or chance. But it does have to do with the imagination and creativeness of a good researcher. It underlies, too, what are called "good leads," for when knowledge in one field reaches a given stage, men in other fields may see how to incorporate that new knowledge or method in fruitful ways. And sometimes they may not: witness the lapse of time between the synthesis of one of the sulfa drugs in 1908 and its successful use in bacterial infections in the thirties. This dependence of some discoveries on antecedent discoveries furnishes the main reason for saying, "You can't just go out and buy the discoveries you want." Some discoveries have cost a good deal of money. But one can't infer from that fact that spending a good deal of money will buy whatever you want. In Professor V. R. Khanolkar's laboratory in Bombay I saw an excellent statement: "Il faut chercher pour trouver mais pas pour trouver ce qu'on cherche"—you must search to find but not to find what you are searching for.—ALAN GREGG, M.D., *Challenges to Contemporary Medicine.* New York, Columbia University Press, 1956, p. 71.

# The Persistence of High Body Sodium in Previously Edematous Patients with Heart Disease

*By* HUGH J. CARROLL, M.D., AND SAUL J. FARBER, M.D.

IN PATIENTS with heart disease the presence of edema is indicative of an increase in extracellular fluid volume. Since the sodium concentration of extracellular fluid is about 140 mEq. per liter, expansion of the extracellular space is accompanied by the accumulation of large quantities of sodium. The magnitude of sodium accumulation has been demonstrated through measurement of total exchangeable sodium in edematous cardiac patients by the sodium-isotope dilution technic.[1-5] When edematous cardiac subjects are rendered free of edema, there is a marked drop in the body content of sodium,[4] but one study showed that in over half of the cases the total exchangeable sodium remains either absolutely high or disproportionately high in terms of the body weight and total body water.[1]

The present investigation was undertaken to re-examine the body composition of the cardiac patient without edema and in particular to determine whether the total body sodium remains elevated or eventually returns to normal levels. The data support earlier observations indicating that the majority of previously edematous cardiac patients have a body content of sodium that is absolutely or relatively high. In addition, the study showed that while some patients gradually lost their sodium excess over a period of months, others maintained a disproportionate elevation in body sodium as long as they were observed.

## Subjects and Methods

In 18 patients with heart disease of various types (table 1) measurements were made of body weight, total body water, and total exchangeable sodium. The measurements were made when the weight of the patients became stable following the loss of edema, and in six of the 18 patients the studies were repeated at intervals for periods of 2 to 5 months.* The diagnosis of congestive heart failure had been made in these patients on the basis of accepted criteria and all had been edematous except one (no. 6). The therapeutic regimen included bed rest, salt restriction, digitalis, and, whenever necessary, diuretics.

Total body water was determined by the antipyrine-dilution technic.[6] Total exchangeable sodium was determined by the dilution technic with $Na^{24}$;[7] 100 microcuries of $Na^{24}$ were injected into the antecubital vein from a calibrated tuberculin syringe. Twenty-four hours were allowed for equilibration and, when the plasma radioactivity had become stable, the counts were recorded. The complete output of urine for the 24-hour period was collected and, if the total radioactivity was greater than 1 per cent of the injected dose, it was subtracted from the injected dose. Plasma and urinary radioactivities were measured with an end-window Geiger-Muller tube. Sodium measurements were made with a Baird internal-standard flame photometer.

The data that are accepted as control values for this study are contained in reference no. 1. They consist of body weight, total exchangeable sodium, and antipyrine space measurements in a group of 27 hospitalized individuals with no evidence of heart disease.

## Results

As a group these patients demonstrated a total body sodium higher than what would have been predicted on the basis of their body weight and total body water. Of the seven patients on whom serial measurements were made, three gradually lost their excess of sodium over a period of months without a fall in body weight or total body water. The remaining four maintained throughout the period of study the same high level of

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*The data from serial studies on a seventh patient, reported in a previous publication from this laboratory, are included in this report.[1]

body sodium that had been observed following compensation.

**Total Body Water (AS)**

The antipyrine space, measured in 14 of the 18 patients, averaged 32.6 liters or 52.2 per cent of the body weight (table 1). The mean figure of 52.2 per cent for body water as the per cent of body weight is the same as that observed in the control group.

**Total Exchangeable Sodium (TENa)**

The mean total exchangeable sodium for this group of 18 patients was 3,140 mEq. (table 1). Although the difference between this level and the mean of 2,896 mEq. in the control group is not statistically significant, it is important to note that the mean body weight of this group was 60.8 Kg. or 6.0 Kg. less than that of the control group (table 5). Twenty patients whose mean body weight was 60.1 Kg. were selected from the control group, and their mean TENa was 2,630 mEq. or 510 mEq. less than that of the cardiac subjects without edema (table 5). It is concluded that there is a significantly larger amount of sodium in the bodies of compensated cardiac patients than in control subjects having the same body weight.

**Body Concentration of Sodium**

Under normal circumstances, the prime determinant of the amount of sodium in the body is the amount of extracellular fluid. In the absence of accurate determination of the extracellular fluid volume the most meaningful expression of body sodium content is in terms of the body weight and total body water. Accordingly, the data are presented as milliequivalents of exchangeable sodium per kilogram of body weight and milliequivalents of exchangeable sodium per liter of water.

**Total Body Sodium/Body Weight**

Seventeen of the 18 patients had ratios of total body sodium/body weight above the normal mean (table 1). The mean ratio for the compensated cardiac subjects was 52.7 mEq. per Kg. as compared with the control level of 43.7, a statistically significant difference.

**Total Body Sodium/Antipyrine Space**

The ratio of body sodium to body water expressed as mEq. per liter was significantly higher 98.3 mEq. per liter, in the compensated cardiac subjects than in the control group 81.3 mEq. per liter (table 1). Of the fourteen patients whose total body water was measured, all had ratios TENa/AS above the normal mean.

**Serial Measurements of Total Exchangeable Sodium and Total Body Water**

In order to determine whether the patient who remains compensated loses his excess sodium, studies were performed at intervals of one to several months in a group of patients whose ratio of total exchangeable sodium to body weight was high following loss of edema. The measurements of body water, TENa, and body weight that were obtained in serial studies of seven such patients are recorded in tables 2 and 3. Three patients showed a fall in TENa over a period of months without a simultaneous loss of body weight or total body water. When normal levels were reached, there was no further fall in TENa. Four patients showed no tendency to lose excess sodium during a comparable period of time. One patient (no. 9) in the latter group gained weight without an increase in total body water (table 3). It is presumed that this gain in weight was in the form of fat.

**Correlation of Sodium Retention with Clinical State**

No correlation was observed between the tendency to maintain or lose excess sodium and such factors as the type of heart disease, age, number of previous episodes of congestive heart failure, the amount of edema previously observed.

## Discussion

The studies of Farber and Soberman (33 patients)[1] and Birkenfeld et al. (3 patients)[5] show that cardiac subjects who have lost edema generally have a higher level of total body sodium than would be predicted on the basis of their body weight. The data from this present study are in agreement with the previously reported findings. It has also been

**Table 1**

*Body Composition in Previously Edematous Cardiac Patients*

| Pt. no. | Sex | Type of* heart disease | Weight (Kg.) | Plasma Na. mEq./L. | Antipyrine space (liters) | Total exchan. sodium (mEq.) | AS† wt. (% body wt.) | TENa† AS (mEq./L.) | TENa† wt. (mEq./Kg.) |
|---|---|---|---|---|---|---|---|---|---|
| 1 | M | RH | 68.0 | 130 | 37.0 | 3,300 | 54.3 | 89.3 | 49.7 |
| 2 | M | RH | 82.3 | 138 | 35.8 | 3,925 | 43.0 | 110.0 | 49.0 |
| 3 | M | AS | 61.5 | 134 | 31.4 | 2,798 | 51.2 | 89.2 | 45.5 |
| 4 | F | RH | 45.5 | 128 | 21.0 | 2,271 | 46.2 | 108.0 | 50.0 |
| 5 | M | ?RH | 55.0 | 133 | 31.0 | 2,670 | 56.2 | 86.5 | 49.3 |
| 6 | M | UNK | 84.5 | 131 | 47.5 | 4,480 | 56.6 | 94.5 | 53.2 |
| 7 | M | RH | 55.0 | 133 | 28.6 | 2,750 | 51.9 | 96.3 | 50.1 |
| 8 | F | AS | 58.0 | 128 | 31.4 | 3,270 | 54.0 | 104.0 | 56.0 |
| 9 | M | UNK | 59.0 | 127 | 36.2 | 3,350 | 61.3 | 96.0 | 57.0 |
| 10 | M | AS | 76.6 | 130 | 32.5 | 2,950 | 42.3 | 91.0 | 38.5 |
| 11 | F | AS | 48.5 | 126 | | 2,680 | | | 55.5 |
| 12 | F | CP | 45.0 | 135 | | 2,860 | | | 63.5 |
| 13 | M | AS | 61.0 | 138 | | 3,335 | | | 55.0 |
| 14 | M | RH | 64.5 | 134 | 32.0 | 3,140 | 49.7 | 98.0 | 48.6 |
| 15 | M | AS | 52.2 | 134 | 28.6 | 3,227 | 54.8 | 113.0 | 62.3 |
| 16 | M | AS | 55.0 | 137 | 32.4 | 2,830 | 58.8 | 87.5 | 51.6 |
| 17 | M | UNK | 57.4 | 130 | | 3,250 | | | 57.0 |
| 18 | M | AS | 60.0 | 132 | 31.4 | 3,345 | 52.2 | 106.0 | 55.5 |
| Mean (N = 18) | | | 60.8 | 132 | 32.6 | 3,140 | 52.2 | 98.3 | 52.7 |
| Standard deviation | | | 11.3 | 3.8 | 7.8 | 497 | 5.5 | 8.85 | 6.1 |
| Standard error | | | 2.7 | .89 | 2.08 | 117 | 1.47 | 2.35 | 1.44 |
| Normal‡ Mean (N = 27) | | | 66.8 | 138 | 35.0 | 2,896 | 52.2 | 81.3 | 43.7 |

*RH, rheumatic heart disease; AS, arteriosclerotic heart disease; UNK, unknown heart disease; CP, cor pulmonale.

†In all tables: AS, antipyrine space; TENa, total exchangeable sodium; TENa/AS, exchangeable sodium per liter of antipyrine space (body water); TENa/wt., exchangeable sodium per Kg. body weight.

‡Data from reference no 1.

shown in this study that previously edematous cardiac patients may retain an increment of sodium for varying periods of time. The mechanism by which this excess quantity of sodium is retained in the body is not readily apparent. Several explanations may be proposed.

If the retained sodium is osmotically active, it must either be in the extracellular space and accompanied by retention of isosmotic quantities of water or in an intracellular compartment in exchange for another cation. Intracellular cations that might be exchanged for sodium include potassium and magnesium.

With regard to the possibility that the excess sodium is in the extracellular space and osmotically active, there are three lines of contrary evidence.

a. The theoretical increase in extracellular water calculated on the possibility that the increment in TENa in each patient is to be explained solely as an augmentation of the extracellular space is shown in table. 4. The assumption was made that the starting extracellular fluid volume is 20 per cent of body weight or 40 per cent of total body water. (The data would not change appreciably if allowance were made for Donnan effect and difference in water content between plasma and extracellular fluid in calculating extracellular sodium concentration.) Table 4 indicates that eight of the 18 patients would have required extracellular space expansion of 41 to 75 per cent over normal, quantities of excess fluid that would probably be detectable in most individuals. No patient in this series

**Table 2**

*Exchangeable Sodium and Body Water in Patients with High Levels of Exchangeable Sodium Following Compensation. Serial Measurements in Patients Whose TENa Fell to Normal*

| Pt. | Date | Wt. (Kg.) | AS (liters) | TENa (mEq.) | TENa/AS (mEq./L.) | TENa/Wt. (mEq./Kg.) |
|---|---|---|---|---|---|---|
| 18 | 3/24/59 | 60.0 | 31.4 | 3345 | 106.2 | 56.0 |
| | 4/14/59 | 61.3 | | 3070 | | 50.0 |
| | 5/21/59 | 62.6 | | 2850 | | 46.0 |
| | 7/28/59 | 62.4 | 34.6 | 2880 | 83.2 | 46.2 |
| W. McL. | 12/11/54 | 61.3 | 32.3 | 4220 | 130 | 68.7 |
| | 1/ 5/55 | 61.4 | 30.6 | 3350 | 109 | 54.5 |
| | 3/16/55 | 61.4 | 32.2 | 2880 | 89 | 47.0 |
| | 4/28/55 | 65.0 | 32.9 | 2600 | 79 | 40.0 |
| 6 | 12/ 3/58 | 84.5 | 47.5 | 4480 | 94.5 | 53.0 |
| | 3/10/59 | 84.5 | 47.0 | 3473 | 74.0 | 41.4 |
| | 4/14/59 | 80.0 | 47.0 | 3400 | 72.5 | 42.5 |

*Comments*

Patient no. 6 lost 4.5 Kg. of body weight after his TENa had fallen to normal. This loss of weight followed a thoracotomy for removal of pericardial calcium and it is thought to represent a loss of fat, since his total body water is unchanged. Hemodynamic studies performed on this patient indicate that congestive heart failure was present and was successfully treated before operation.

Patient no. 18 gained a small amount of weight and an approximately equal amount of water during the study. At the same time his TENa continued to fall toward normal and stabilized in the normal range.

*The data on patient W. McL. were published in a previous report.[1]

had demonstrable fluid collections in the extremities, sacrum, or peritoneal, pleural, or pericardial space when body sodium and water were measured.

b. The concept that an increase in body sodium represents an increased extracellular fluid volume is challenged by the observation on the three compensated cardiac subjects who showed a gradually diminishing TENa without a concomitant loss of body weight or body water. These three patients, nos. 18, 6, and W. McL. (table 2), lost respectively 500, 1,600, and 1,000 mEq. of sodium. It seems likely that if such quantities of sodium were in the extracellular space, clinical edema would have been apparent.

c. The total body water as the per cent of body weight is normal in compensated cardiac subjects, so that any excess of extracellular water would occur at the expense of the intracellular fluid. If larger quantities of water were to leave the intracellular space, a marked reorganization of intracellular osmotically active cation would be required. This might be accomplished in several ways.

1. Intracellular potassium might become osmotically inactive, a possibility that cannot at present be ruled out.

2. The intracellular osmolarity might be much greater than the extracellular osmolarity, an event that would contradict good physiologic evidence.

3. Intracellular potassium might be markedly depleted. Since most of the body potassium is intracellular, this would necessitate marked depletion of body potassium. Evidence against this possibility is cited below.

If the excess of sodium in the compensated cardiac patient were in an intracellular site in place of potassium, the majority of subjects would be profoundly depleted of potassium. Total body potassium was not measured in these patients. The literature contains studies on the metabolism of potassium in congestive heart failure that indicate a depletion of body potassium in the edematous phase but this deficit probably does not exist when the pa-

**Table 3**

*Exchangeable Sodium and Body Water in Patients with High Levels of Exchangeable Sodium Following Compensation. Serial Measurements in Patients Whose TENa Remained Elevated*

| Pt. | Date | Wt. (Kg.) | AS (liters) | TENa (mEq.) | TENa/AS (mEq./L.) | TENa/Wt. (mEq./Kg.) |
|---|---|---|---|---|---|---|
| 15 | 4/14/59 | 52.2 | 28.6 | 3227 | 113.0 | 62.3 |
| | 5/21/59 | 52.6 | | 3317 | | 63.0 |
| | 6/16/59 | 54.5 | | 3210 | | 59.0 |
| 12 | 1/13/59 | 45.0 | | 2860 | | 63.5 |
| | 3/ 4/59 | 45.0 | | 2730 | | 60.7 |
| 9 | 12/17/58 | 59.0 | 36.2 | 3350 | | 57.0 |
| | 4/ 1/59 | 66.5 | 36.7 | 3500 | 95.3 | 52.6 |
| | 4/14/59 | 66.5 | | 3600 | | 53.0 |
| 16 | 1/ 7/59 | 55.0 | 32.4 | 2830 | 87.5 | 51.6 |
| | 3/ 4/59 | 55.0 | 31.3 | 2980 | 95.4 | 54.2 |
| | 6/ 3/59 | 55.0 | 30.3 | 2812 | 93.5 | 51.2 |

*Comments*

Patient no. 15 required repeated injections of mercurials in order to maintain his dry weight. He gained about 1 Kg. of water weekly but never demonstrated edema or other signs of frank decompensation.

Patient no. 9 gained 7.5 Kg. of weight during the study without a change in TENa. Since there was no change in his total body water, it is presumed that this increase in weight represents very largely an accumulation of fat.

tients become free of edema.[8-11] Measurements of total exchangeable potassium in compensated cardiac subjects were made by Birkenfeld et al. and by Aikawa and Fitz. The total exchangeable potassium levels in these patients were in the range of those found by Birkenfeld et al. in a series of hospitalized patients with no evidence of heart disease.[4, 10] The compensated cardiac patients have been compared with the general hospital population because they are chronically ill and it would be unreasonable to compare their total body electrolytes with those of normal persons. The evidence reviewed appears to support the view that the compensated cardiac patients are merely sick people with no specific deficit of total body potassium.

Measurements of the external balance of magnesium in five patients during recovery from congestive heart failure were made by Mader et al.[10] It was shown that the magnesium balance may be positive or negative, but only small quantities of this cation are involved. It appears improbable that the retention of large quantities of sodium can be explained by depletion of potassium or magnesium.

It is possible that strategic combinations of occult edema and potassium depletion in the same patient might explain sodium retention by some compensated cardiac patients, especially if the amount of sodium retained is small. Another solution, however, is compatible with the data. Some of the sodium may be osmotically inactive.

If the sodium is osmotically inactive, it may be bound to some intracellular constituent or to an extracellular constituent of tissues such as bone, cartilage, or connective tissue.

There is some evidence that intracellular constituents such as nucleotides can bind sodium in an osmotically inactive form in vitro, but there are no studies of the physiologic importance of this binding.[12]

The possibility of sodium storage in bone in disease states has recently been studied. Bone sodium concentration was measured in a series of patients who died with a variety of electrolyte disorders including heart disease, and no abnormality in bone sodium concentration was demonstrated.[13]

Connective tissue and cartilage are known to be capable of storing cations in an osmotically inactive state and of acting as ion exchangers.[14, 15] These tissues are rich in chondroitin sulfate, a long chain polyanion,

**Table 4**

*Theoretical Calculations*

| Pt. No. | "Extra"* exch. Na mEq. | AS | Calculated extracellular space (liters) | | % "Extra" ECF† | |
|---|---|---|---|---|---|---|
| | | | As 40% of AS | As 20% of body wt. | On basis of AS | On basis of body wt. |
| 1 | 400 | 37.0 | 14.8 | 13.6 | 20.4 | 22.2 |
| 2 | 440 | 35.8 | 14.3 | 16.0 | 19.8 | 17.8 |
| 3 | 120 | 31.4 | 12.6 | 12.3 | 8.4 | 8.4 |
| 4 | 290 | 21.0 | 8.4 | 9.1 | 28.0 | 25.8 |
| 5 | 310 | 31.0 | 12.4 | 11.0 | 19.0 | 21.1 |
| 6 | 800 | 47.5 | 19.0 | 16.9 | 32.7 | 37.0 |
| 7 | 355 | 28.6 | 11.4 | 11.0 | 26.3 | 27.4 |
| 8 | 720 | 31.4 | 12.6 | 11.6 | 49.7 | 54.0 |
| 9 | 785 | 36.2 | 14.5 | 11.8 | 49.0 | 59.7 |
| 10 | ‡ | | | | | |
| 11 | 585 | 25.2§ | 10.1 | 9.7 | 47.3 | 49.2 |
| 12 | 900 | 23.4§ | 9.36 | 9.0 | 73.6 | 77.5 |
| 13 | 690 | 31.7§ | 12.7 | 12.2 | 40.0 | 41.3 |
| 14 | 320 | 32.0 | 12.8 | 12.9 | 20.9 | 20.9 |
| 15 | 970 | 28.6 | 11.4 | 10.44 | 65.5 | 72.8 |
| 16 | 440 | 32.4 | 12.9 | 11.0 | 26.7 | 31.6 |
| 17 | 790 | 30.0§ | 12.0 | 11.5 | 45.0 | 47.0 |
| 18 | 770 | 31.4 | 12.6 | 12.0 | 43.3 | 45.7 |

*Observed TENa minus normal TENa (Body wt. × 43.7 mEq.).

†"Extra" exch. Na divided by plasma Na concentration gives the number of liters of water required to contain this amount of Na at a concentration equal to plasma. This number of liters divided by the extracellular fluid volume equals the % "Extra" ECF.

‡This patient's TENa was below normal.

§AS could not be measured. This figure represents 52.2% of body weight.

**Table 5**

*Summary of Mean Values and Statistical Analysis*

| | Compensated cardiac patients (N = 18) | Controls (N = 27) | p* Controls vs. compensated cardiac patients | Controls with same body weight (N = 20) | p Controls with same body weight vs. compensated cardiac patients |
|---|---|---|---|---|---|
| Weight (Kg.) | 60.8 | 66.8 | NS‡ | 60.1 | NS |
| Antipyrine space (liters) | 32.6† | 35.0 | NS | 32.8 | NS |
| TENa (mEq.) | 3140 | 2896 | NS | 2630 | >0.01 |
| TENa/AS (mEq./L) | 98.3† | 81.3 | >0.01 | 81.3 | >0.01 |
| TENa/wt. (mEq./Kg.) | 52.7 | 43.7 | >0.01 | 44.7 | >0.01 |

*$p$ = Probability of t.[17]

†N = 14.

‡NS = not significant.

and in the case of cartilage at least, the cation-binding capacity of the tissue appears to depend upon its chondroitin sulfate content.[13] The ability of chondroitin sulfate to bind sodium has been demonstrated by equilibrium dialysis studies with sodium chondroitin sulfate isolated from bovine nasal cartilage.[16] In these studies a significant portion of the sodium associated with the polyanion failed to behave as osmotically active ion. It appears possible that sodium binding by chondroitin sulfate may be of importance in those disease states in which storage of osmotically inactive sodium is thought to occur.

The fact that compensated cardiac patients generally have a TENa higher than would be predicted on the basis of body weight and total body water may be taken as evidence that in patients with heart disease sodium retention need not be accompanied by equivalent water retention. Further support for this view may be found in the observation that compensated cardiac subjects with high TENa may lose large quantities of sodium without losing water as they remain in a compensated state. Retention and loss of sodium without concomitant changes in body water suggest that sodium may enter some tissue where it is bound in an osmotically inactive form. The evidence that chondroitin sulfate can bind sodium and the widespread occurrence of chondroitin sulfate in the connective tissues of man make it reasonable to postulate that storage of osmotically inactive sodium in connective tissue may be an important feature of heart disease.

**Summary**

Measurements of total body water and total exchangeable sodium were made in patients with heart disease rendered free of edema following congestive heart failure.

The total exchangeable sodium in most of the patients was higher than would have been predicted on the basis of their body weight and total body water. Serial measurements showed that some patients gradually lose their excess sodium over a period of months without a loss of body water; others maintain an elevated ratio of body sodium to body weight and body sodium to body water for periods of at least several months.

The data imply the possibility of significant quantities of osmotically inactive sodium in patients with heart disease.

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# Studies on Starling's Law of the Heart

## IV. Observations on the Hemodynamic Functions of the Left Atrium in Man

*By* EUGENE BRAUNWALD, M.D., AND CHARLES J. FRAHM, M.D.

". . . and, if at this time, with its auricle alone beating, you cut off the apex of the heart with a pair of scissors, you will see the blood flow out from the wound with each beat of the auricle. You will thus realize that the blood gets into the ventricles not through any pull exerted by the distended heart, but through the driving force exerted by the beat of the auricles."[1] William Harvey, 1628.

SINCE THE OBSERVATIONS of Harvey described above were carried out, several investigators, employing a variety of different experimental preparations, have demonstrated quite clearly that the rate of ventricular filling is augmented during atrial contraction.[2-6] It is the purpose of this communication to demonstrate the clinical importance of atrial contraction in patients in whom left ventricular function is disturbed. In such patients atrial contraction raises left ventricular end-diastolic (filling) pressure (LVEDP) without a concomitant elevation of the mean left atrial pressure (MLAP). Since, in accordance with Starling's law of the heart,[7] the characteristics of ventricular contraction are a function of the ventricular end-diastolic fiber length and pressure, the atrium, by its effects on LVEDP and left ventricular end-diastolic fiber length is capable of modifying the performance of the ventricles.

Elevations of LVEDP may result from an impairment of myocardial contractility, from an increased hemodynamic burden placed on the left ventricle, from altered diastolic distensibility of this chamber, or from a combination of these factors. If, for example, in a patient with an abnormality of left ventricular function the LVEDP is elevated to 25 mm. Hg, without atrial contraction the MLAP must also be in the neighborhood of 25 mm. Hg, in order to fill the ventricle to this end-diastolic pressure. Similarly, the pulmonary venous and pulmonary capillary pressures must be approximately 25 mm. Hg, or slightly higher, and these levels of pressure might well result in symptoms of pulmonary congestion. A mechanism that could maintain the LVEDP at the level necessary for an effective left ventricular contraction, while permitting the MLAP and therefore the pulmonary capillary pressure to remain at a lower level, would be of clinical benefit. A vigorous left atrial contraction occurring just prior to ventricular contraction could provide such a mechanism.

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### Methods

A total of 42 patients was studied by means of transseptal left heart catheterization.[8] All patients, unless specified, had normal sinus rhythm with a P-R interval less than 0.20 second and none had any clinical or hemodynamic evidence of mitral valve involvement. Twenty-six patients had abnormalities of left ventricular function and were considered, on clinical grounds, to have serious or hemodynamically significant lesions. All 26 patients had roentgenographic evidence of left ventricular enlargement and all had symptoms that were thought to be related to their heart disease. They ranged in age from 6 to 62 years and averaged 35 years. The etiology of the abnormal left ventricular function was aortic stenosis in 16 patients, aortic regurgitation in one patient, combined aortic stenosis and regurgitation in four patients, coronary artery disease in two patients, and left ventricular hypertrophy of unknown etiology in three patients.

Sixteen subjects with normal cardiovascular systems were studied. They ranged in age from 5 to 49 years, and averaged 21 years. None of them had symptoms related to the heart but all had heart murmurs that were considered to be of functional origin. The findings at right and left heart catheterization were within normal limits. In five of these subjects 1,500 ml. of blood were withdrawn over a 10-day period and this blood was reinfused at the time of study in order to elevate the LVEDP and MLAP. Both the left

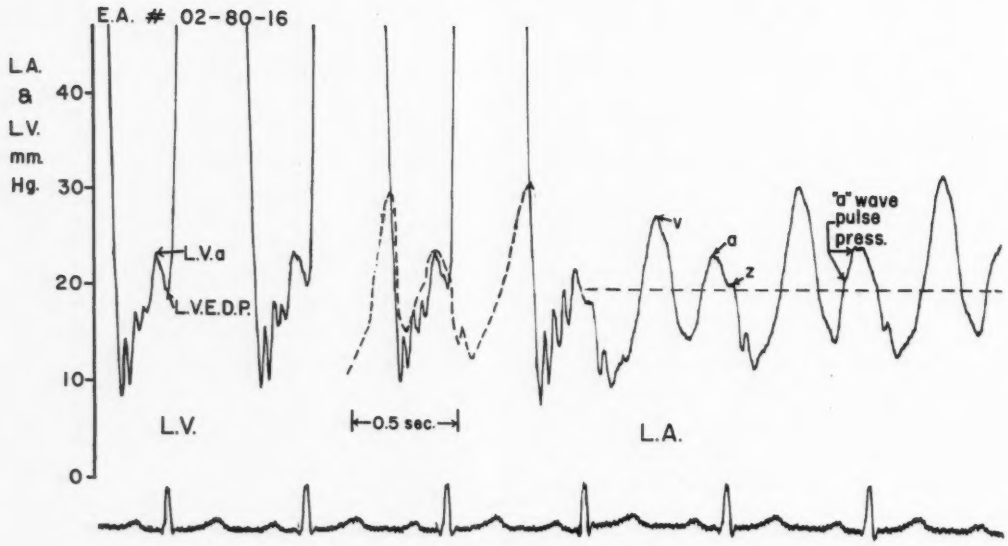



**Figure 1**

*Continuous pressure tracing recorded as the catheter was withdrawn from the left ventricle (L.V.) into the left atrium (L.A.) in a patient without heart disease whose intracardiac pressures had been elevated with a blood transfusion. LVEDP represents the left ventricular end-diastolic pressure. LVa represents the transmission of the atrial contraction wave into the left ventricle. The broken line near a segment of the left ventricular pressure pulse represents a superimposed left atrial pressure pulse. The broken horizontal line through the left atrial pressure pulse represents the mean atrial pressure.*

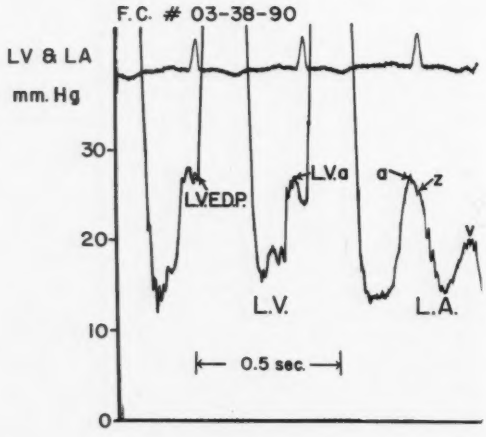



**Figure 2**

*Pressure pulses recorded as the catheter was withdrawn from the left ventricle (L.V.) to the left atrium (L.A.) in a patient with left ventricular hypertrophy of unknown etiology. Other symbols same as in figure 1.*

ventricular and the left atrial pressures were suitable for analysis in 21 patients and 15 subjects; in five patients and in one subject only the left atrial pressure pulse could be analyzed.

In the 36 patients in whom both left atrial and left ventricular pressures were analyzed, these were recorded in rapid succession as the catheter was withdrawn from the left ventricle to the left atrium. Two representative pressure tracings are illustrated in figures 1 and 2. Each value for LVEDP, left atrial "z" point,[9] and "a" wave pressures reported below represents the average of all beats during two complete respiratory cycles; in no instance was LVEDP calculated from the LA "z" point pressure. MLAP was determined by planimetric integration of the same beats utilized for the measurement of left atrial "z" point pressure. Evidence for the close correspondence between the left atrial "z" point pressure and the LVEDP has been presented elsewhere.[10] Previous studies had demonstrated that the time interval between the onset of the QRS and of left ventricular contraction equals 0.05 second.[11] This interval was employed in defining the LVEDP and the left atrial "z" point pressure.

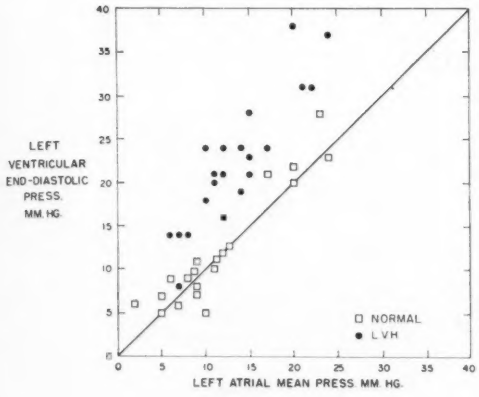



**Figure 3**

*Relationship between left ventricular end-diastolic and mean left atrial pressure. The oblique line represents the line of identity. The distance of each point from this line represents the difference between LVEDP and MLAP.*

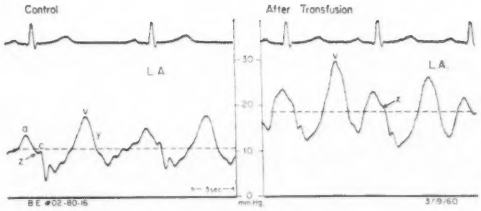



**Figure 4**

*Left atrial pressure pulse obtained from a subject with a functional heart murmur before* (left) *and after (right) blood transfusions. The broken lines represent the MLAP. It is apparent in both tracings that the "z" point pressure (and LVEDP) occur after atrial contraction has been completed and that, therefore, the MLAP and "z" point pressures are almost identical.*

## Results

The relationship between LVEDP and MLAP is illustrated in figure 3. In the subjects with normal cardiovascular systems, LVEDP-MLAP ranged from +4 to –5 mm. Hg and the difference between these two pressures averaged 0.2 mm. Hg. In the five subjects in whom these pressures were elevated by means of acutely induced hypervolemia, MLAP averaged 21 mm. Hg and LVEDP-MLAP averaged 2 mm. Hg. Thus, in the subjects with normal cardiovascular systems left atrial contraction did not result in an elevation of LVEDP without a concomitant elevation of MLAP. A representative left atrial pressure pulse obtained from one of these subjects before and after blood transfusion is reproduced in figure 4.

In all 21 patients with left ventricular disease the LVEDP exceeded MLAP; this pressure difference ranged from 1 to 18 mm. Hg and averaged 9.0 mm. Hg. Thus, in these patients left atrial contraction elevated LVEDP while permitting the MLAP to remain at a lower level. Representative left atrial pressure pulses obtained from patients with idiopathic left ventricular hypertrophy are reproduced in figures 2 and 5. It is clear that in these patients the left atrial "z" point pressure, (i.e., the atrial pressure at the onset of ventricular contraction[9]) exceeds the MLAP. A representative left ventricular pressure pulse obtained from a patient with aortic stenosis is reproduced in figure 6; the elevation of left ventricular diastolic pressure brought about by left atrial contraction is clearly evident.

The influence of atrial contraction on the relationship between the MLAP and the left atrial "z" point pressure is also evident in the pressure tracings obtained from patient A.C., a 55-year-old woman with impairment of left ventricular function due to coronary artery disease, who developed a brief bout of atrial fibrillation in the course of the catheterization; left atrial pressure and cardiac output were measured with the patient in sinus rhythm and during fibrillation (fig. 7). At the time the patient exhibited a normal sinus mechanism the MLAP equaled 4 mm. Hg, there was a prominent "a" wave and the "z" point pressure occurred at the peak of the "a" wave, i.e., its average value was 10 mm. Hg; the cardiac output, measured by the dye-dilution technic, equaled 3.10 L. per minute. After atrial fibrillation had developed, however, MLAP had to rise to 8 mm. Hg in order to maintain the left atrial "z" point pressure (and the LVEDP) at levels that averaged 8 mm. Hg. The cardiac output during atrial fibrillation was 2.90 L./min. and the

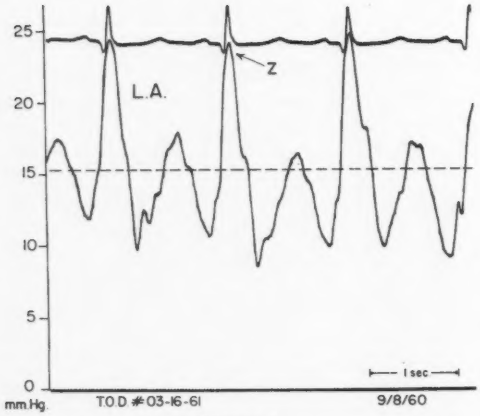



**Figure 5**

*Left atrial pressure pulse in a patient with left ventricular hypertrophy of unknown etiology. The tall waves are the "a" waves, and the "z" point occurs near the peak of the "a" wave, before atrial relaxation has occurred.*

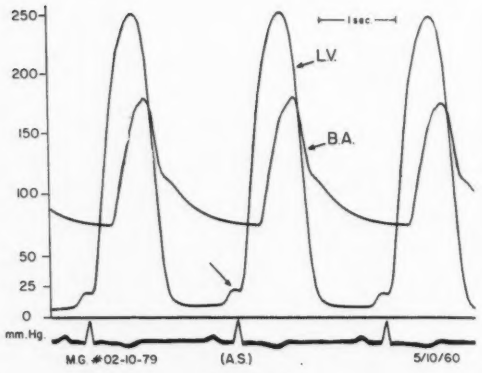



**Figure 6**

*Simultaneously recorded left ventricular (LV) and brachial artery (BA) pressure pulses obtained from a patient with aortic stenosis. The arrow indicates the elevation of ventricular diastolic pressure resulting from atrial contraction.*

systemic arterial pressure was unchanged from that obtained when the patient was in sinus rhythm.

Further evidence of the importance of the contribution of atrial contraction to ventricular filling was obtained from the pressure tracings obtained from patient C.B., a 52-year-old man with aortic stenosis, who developed a brief bout of atrioventricular dissociation in the course of the left heart catheterization. In the tracing illustrated in figure 8, in the first beat, atrial systole occurred at a normal time in relation to ventricular systole. (P-R = 0.19 second) : in the second beat atrial systole moved closer to the onset of ventricular systole (P-R = 0.13 second), during the third beat both chambers contracted simultaneously, and in the fourth beat atrial contraction followed ventricular contraction (R-P = 0.13 second). The LVEDP was highest during the first beat, in which the atrial contribution to ventricular filling was maximal, and as the temporal relationship between atrial and ventricular systole became progressively more abnormal, the LVEDP fell. The strength of ventricular contraction (as reflected in the left ventricular peak systolic pressure, the brachial artery systolic and pulse pressures, the peak left ventricular-brachial artery pressure gradient, the duration of mechanical systole and the tension-time index[12]) declined, as LVEDP fell. Thus, in spite of the fact that the ventricular rate remained constant, the characteristics of ventricular contraction were apparently determined by the contribution of atrial systole to ventricular filling, which, in turn, was a function of the temporal relationship between atrial and ventricular systole.

An attempt was made to identify the mechanisms responsible for the ability of the left atrium to raise the left atrial "z" point pressure and LVEDP above the level of the MLAP. Inspection of the pressure tracings revealed that in the patients with left ventricular disease in whom this occurred the atrial contraction ("a") waves were particularly prominent and dominated the left atrial pressure pulse; it was also apparent that at the instant at which the left ventricle began to contract, i.e., at the time of the left atrial "z" point pressure, the left atrium was still in systole, that is the left atrial "z" point pressure corresponded closely, both in time and amplitude, with the peak of the "a" wave pressure (figs. 2, 5, and 7).

In the patients with left ventricular dis-

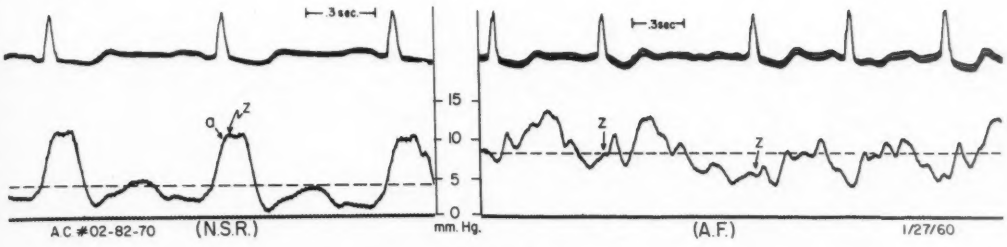



**Figure 7**

*Left atrial pressure pulses obtained from patient A.C. The tracing on the left was obtained during normal sinus rhythm (N.S.R.); the tracing on the right was obtained during atrial fibrillation (A.F.)*

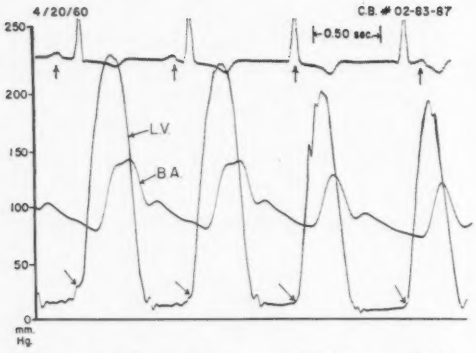
ease, as the pressure at the onset of atrial contraction increased, the "a" wave pulse pressure (the difference between the pressures at the onset and peak of the "a" wave) also tended to increase (fig. 9). It would thus appear likely that the amplitude of the "a" wave is a function of the pressure in the left atrium existing at the onset of atrial contraction.

The duration of left atrial contraction exhibited a tendency to be greater in the patients with left ventricular disease than in the normal subjects. The time interval between the onset and peak of the atrial contraction wave in the normal subjects averaged .055 second and it did not exceed .08 second in any of them, whereas in the patients with left ventricular disease this time interval averaged .087 second and in 12 of the 26 patients it exceeded .08 second (fig. 10). The contribution of left atrial contraction to the left atrial "z" point pressure (or LVEDP) appeared to be related to the duration of atrial contraction. The relationship between the time interval from the onset to the peak of the "a" wave, and the pressure rise from the onset of the "a" wave to the "z" point pressure (the "atrial kick") is plotted in figure 11. In the normal subjects, in whom the duration of atrial contraction tended to be shorter than in the patients with left ventricular disease, the "atrial kick" did not exceed 2 mm. Hg; the "atrial kick" became progressively larger in the patients with left ventricular disease as the duration of atrial contraction became prolonged.

The manner in which the duration of atrial contraction modified the atrial contribution to the left atrial "z" point and therefore the LVEDP is apparent from examination of figure 12. Since the P-R intervals were within normal limits in all patients included in this study, the time interval from the onset to the peak of the "a" wave varied inversely with the time interval from the peak of the "a" wave to the onset of ventricular contraction. When atrial contraction was prolonged, and the time interval between the peak of the "a" wave and the onset of left ventricular contraction was short or even absent, the left atrial "z" point pressure and LVEDP were elevated, since they occurred before the atria relaxed. On the other hand in the normal subjects, with a shorter time interval between the onset and peak of the "a" wave (fig. 10) ventricular contraction commenced when atrial relaxation was almost or entirely completed, the left atrial "z" point pressure and the LVEDP were at approximately the same level as the atrial pressure at the onset of atrial contraction (i.e., the atrial "kick" was absent or small).

## Discussion

Although the importance of the contribution of atrial contraction to ventricular filling was first suggested by William Harvey,[1] investigators in the early part of this century attributed little hemodynamic significance to




| | | | | |
|---|---|---|---|---|
| L.V., s/d | 233/30 | 225/21 | 202/15 | 194/12 |
| B.A., s/d | 142/79 | 139/80 | 128/82 | 120/72 |
| GRAD. | 91 | 86 | 74 | 74 |
| DUR. SYS. | .43 | .40 | .36 | .32 |
| T.T.I. | 72 | 65 | 48 | 42 |

**Figure 8**

*Simultaneously recorded left ventricular (L.V.) and brachial artery (B.A.) pressure pulses obtained from a patient with aortic stenosis and atrioventricular dissociation. The vertical arrows near the top point to the P waves on the electrocardiogram; the oblique arrows near the bottom of the tracing indicate the left ventricular end-diastolic pressure. The figures below each beat indicate the pertinent hemodynamic measurements. S/d = systolic/diastolic pressures in mm. Hg. GRAD. = pressure gradient in mm. Hg between the peak left ventricular and peak brachial artery pressures. DUR. SYST. = Duration of systole in seconds, between onset of ventricular contraction and aortic valve closure. T.T.I. = Tension-time index in mm. Hg-sec.*[10]

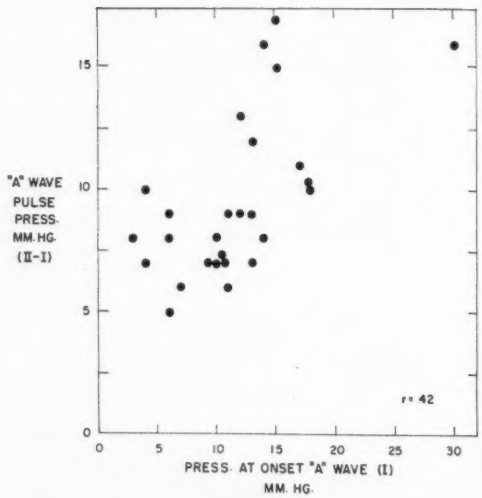



**Figure 9**

*Relationship between pressure at onset of "a" wave and the "a" wave pulse pressure. The latter is represented by the difference between the peak of the "a" wave pressure and that at the onset of the "a" wave.*

atrial systole, but considered the functions of the atria to be the storage of blood, the initiation and propagation of the impulse of depolarization, and the closure of the atrioventricular valves.[13] Sir Thomas Lewis, in his classic experimental studies on the circulatory effects of atrial fibrillation, attributed the hemodynamic changes following the onset of this arrhythmia (decline in aortic pressure and cardiac output, and elevation of venous pressure) to be secondary to the increase in ventricular rate rather than to the loss of atrial contraction.[14] Similarly, Yandell Henderson considered the atria to be of minor importance as contractile organs and expressed the opinion that if atrial systole did force blood into the ventricles, it was a few drops at most.[15] It remained to Gesell, in a series of detailed experimental studies on the dynamics of atrial systole, to establish the hemodynamic importance of the atria.[3, 16-18] He observed, in heart-lung preparations, that at any given venous filling pressure, atrial contraction could augment ventricular filling and therefore cardiac output by an amount that approximated 50 per cent of that resulting from passive venous filling alone.[18] Atrial systole elevated ventricular end-diastolic tension and fiber length, thereby resulting in a more forceful and prolonged ventricular contraction.[17] Gesell also demonstrated quite clearly that the effectiveness of atrial systole in augmenting ventricular output is dependent upon the time relationship between atrial and ventricular systole; the greatest effect on ventricular filling occurred when atrial contraction was completed .008 to .020 second before the onset of ventricular contraction.[3] Wiggers and Katz, utilizing a cardiometer, showed that atrial systole contributed 18 to 60 per cent of the total volume of blood that entered the

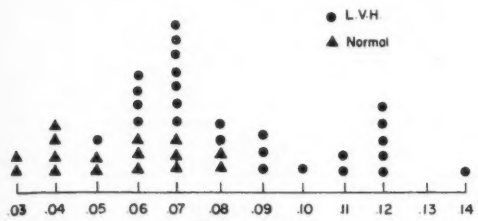



**Figure 10**

*Time intervals between the onset and peak of the "a" waves.*

ventricles during diastole.[4] Jochim, in experiments on dogs with complete heart block, demonstrated that if atrial relaxation occurred before ventricular contraction commenced, a significant fraction of the blood contributed by atrial systole regurgitated from the ventricle back to the atrium.[5] However, pertinent to the data presented in figures 8 and 12, he also found that the atrial contribution to ventricular filling was much greater when atrial contraction began only 0.08 to 0.13 second before the onset of ventricular contraction, since under these circumstances ventriculo-atrial regurgitation could not take place.

In regard to the determinants of the strength of atrial contraction, it appears that Starling's law of the heart applies to the atrium as well as to the ventricle. Utilizing three different experimental preparations, Gesell,[16] Prinzmetal,[19] and Blinks[20] have shown that the characteristics of atrial contraction are determined by the length of the atrial fibers just prior to systole. The data presented in figure 9 are consonant with the view that the characteristics of left atrial contraction in man are also determined by the pressure existing in that chamber at the onset of its contraction. As Sarnoff and his collaborators[21] have recently demonstrated, however, the strength of atrial contraction is also influenced profoundly by the sympathetic nerves and the vagi. In addition, these investigators have shown that the carotid sinuses are important in the reflex control of atrial contractility,[22] and that the relationship between MLAP and ventricular stroke work is determined by the performance characteristics of the atrium as well as of the ventricle.[23]

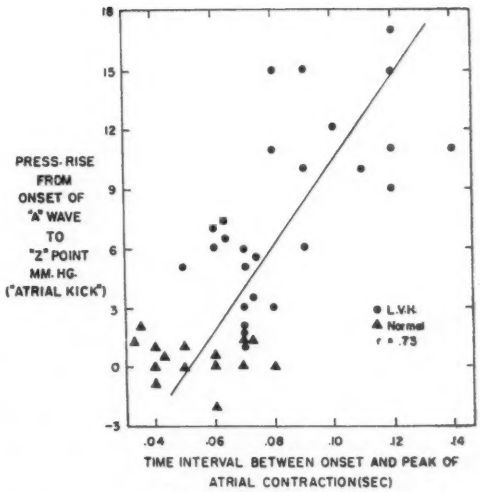



**Figure 11**

*Relationship between time interval from onset to peak of "a" waves and the "atrial kick."*

Previous studies on the effects of atrial contraction in man have been concerned primarily with the changes in cardiac output that usually occur when patients with atrial fibrillation[24-26] or atrial flutter[27] are reverted to sinus rhythm, and with the contribution of atrial systole to ventricular filling in patients with heart block.[28] In the present investigation, attention was focused on the effects of atrial systole on the relationship between LVEDP and MLAP. The physiologic importance of the LVEDP is implicit in the concept of ventricular function of Sarnoff and his collaborators, who have shown[21] that, with any given catecholamine stimulus, the contraction of the ventricle varies directly with the end-diastolic pressure (and fiber length). Thus, each heart requires a specific end-diastolic pressure (and fiber length) to contract in a particular manner. The physiologic and clinical importance of the mean atrial pressure is clear when it is considered that many of the manifestations of cardiac failure result directly or indirectly from an elevation of atrial pressure and of the pressures in venous and capillary beds proximal to the atrium. Thus, while the ventricular end-diastolic pressure may be considered to be the hemody-

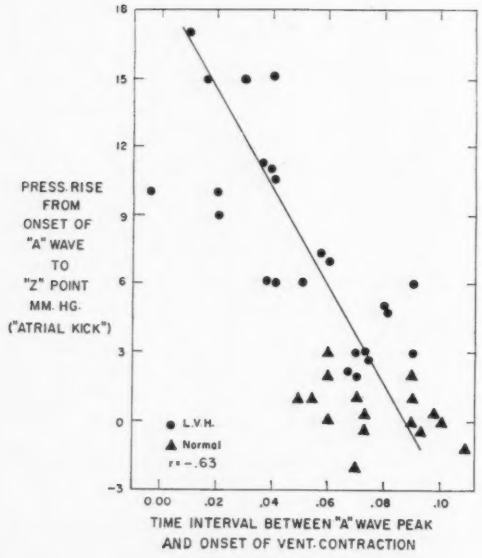



**Figure 12**

*Relationship between time interval from "a" wave peak and the onset of ventricular contraction and the "atrial kick."*

namic "stimulus" that determines the force of ventricular contraction, the mean atrial pressure may be considered to be the hemodynamic "price" that the organism must pay in order to provide this stimulus. In view of these considerations the relationship between LVEDP and MLAP is considered to be a meaningful one.

In subjects with normal cardiovascular systems, although atrial systole may augment the rate of ventricular filling, it does not raise LVEDP above MLAP when these pressures are at normal levels and after they have been elevated by blood infusions (figs. 1 and 3). In contrast, in patients with left ventricular disease and elevation of the LVEDP, left atrial systole is responsible for maintaining MLAP at a level significantly lower than the LVEDP (figs. 2, 3, and 5). The specific mechanism by which atrial systole results in this discrepancy between LVEDP and MLAP is not entirely clear; but a number of the factors, including the force and duration of atrial contraction, appear to be of importance. The force of atrial contraction, as reflected by the pulse pressure of the "a" wave was substantially greater in the patients with left ventricular disease than it was in normal subjects, and the height of the "a" wave was related to the atrial pressure prior to the onset of atrial contraction (fig. 9). The duration of atrial contraction was found to be longer in the patients with left ventricular disease than in the normal subjects (fig. 10), the "atrial kick" varied directly with the time interval between the onset and peak of the "a" wave (fig. 11) and inversely with the time interval between the "a" wave peak and the onset of ventricular contraction (fig. 12).

It is apparent, from a consideration of the pressure-volume curves of the ventricle[6] that in spite of the elevation of LVEDP produced, the volume of blood contributed by atrial systole to ventricular filling may not be greater than normal in the patients with left ventricular disease, since in these patients the thickened left ventricular wall presumably results in a diminished ventricular compliance. Regardless of the actual volume of blood contributed by the atrium, when atrial contraction ceases (fig. 7) or when its temporal relationship to ventricular contraction is disturbed (fig. 8), the circulatory response is an elevation of the MLAP (fig. 7), a decline in the force of ventricular contraction (fig. 8), or a combination of both of these. The importance of maintaining normal sinus rhythm in patients with left ventricular disease is therefore evident.

Data obtained in the present investigation are also pertinent to a consideration of the applicability of Starling's law of the heart to be human left ventricle. In a recent study carried out on patients with mitral stenosis and atrial fibrillation, it was shown that the characteristics of ventricular contraction are a function of left ventricular end-diastolic segment length and of the LVEDP.[29] In these patients, variations in the ventricular rate were responsible for alterations in LVEDP, and the possibility that these variations in rate could have been responsible for the changes in the characteristics of ventricular

contraction could not be excluded. The observations illustrated in figure 8 are pertinent to this problem; the strength of ventricular contraction, as measured by the peak left ventricular pressure, the brachial artery pulse pressure, the duration of systole, and the tension-time index all varied directly with the LVEDP, in spite of a constant ventricular rate. These observations thus further support the concept, previously expressed,[29] that Starling's law is operative in the heart of intact man.

**Summary**

The hemodynamic functions of the left atrium were studied in 26 patients with disturbances of left ventricular function and in 16 subjects without any abnormalities of the cardiovascular system. Attention was directed to the effect of atrial systole on the relationship between mean left atrial pressure (MLAP) and left ventricular end-diastolic pressure (LVEDP). This relationship was considered to be a meaningful one in view of the importance of the LVEDP in determining the characteristics of ventricular contraction, and of the MLAP in determining the symptoms of left heart failure. In the subjects with normal cardiovascular systems, LVEDP-MLAP averaged 0.2 mm. Hg, but this value averaged 9.0 mm. Hg in patients with left ventricular disease, in whom left atrial contraction elevated LVEDP while permitting MLAP to remain at a significantly lower level. The magnitude of the pressure difference between LVEDP and MLAP was found to be dependent on the characteristics of atrial contraction; the height of the "a" wave appeared to be related to the atrial pressure prior to the onset of atrial contraction. The elevation of atrial pressure produced by atrial systole was found to vary directly with the time interval between the onset and the peak of the "a" wave and to vary inversely with the time interval between the peak of the "a" wave and the onset of ventricular contraction. Evidence was presented that in intact human subjects the characteristics of left atrial and left ventricular contraction are functions of the pressures in these chambers prior to the onset of their contraction, thus lending further support to the concept that Starling's law is operative in the human heart.

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## On Cardiac Murmurs

*By* AUSTIN FLINT, M.D.

The mitral direct is a pre-systolic murmur; this name expresses its proper relation to the heart sounds, and it is the only murmur which does occur in that particular relation. The time of its occurrence as just explained, and as expressed by the term pre-systolic, is sufficient for its easy recognition when once it is fully comprehended.—*Am. J. M. Sc.* n.s. 44: 29, 1862.

# Computer Analysis of Electrocardiographic Measurements

*By* ARTHUR E. RIKLI, M.D., WALTER E. TOLLES, C. A. STEINBERG, W. J. CARBERY, ALVIN H. FREIMAN, M.D., SIDNEY ABRAHAM, AND CESAR A. CACERES, M.D.

AS COMPUTERS are found to have useful medical applications, we must recognize that a computer is limited to designated functions. The computer can retain an almost unlimited number of facts, and can associate and tabulate those facts in any manner a programmer directs. Some people hope and others fear that computers will reduce the need for certain types of medical skills. There is no serious reason for physicians to be concerned in this regard. The computer can only process the information provided to it by the physician and then the physician must determine how to use the results of the computer's effort, in the same way that he uses the results from other diagnostic aids. It is practical to suggest that use of a computer for processing selected objective data can sharpen the physician's diagnostic capabilities and result in better medical care for his patients.

The purpose of this study was to explore the use of a properly programmed computer to distinguish clinically identifiable normal and abnormal electrocardiograms. This type of procedure, if practical, could be used as an aid in diagnosis by physicians.

### Materials and Methods

A total of 45 persons was included in this study, of whom 31 were male and 14 were female. Fifteen subjects had clinically normal cardiovascular systems with no murmurs, with blood pressures less than 140/90, and with normal 12-lead electrocardiograms and chest x-rays. Fifteen subjects were hypertensive with resting fixed systolic pressures of 160 mm. Hg or more and a diastolic blood pressure above 90 mm. Hg. Electrocardiographic evidence compatible with left ventricular hypertrophy, according to Sokolow and Lyon,[1] and x-ray evidence of left ventricular hypertrophy were required. Fifteen subjects had aortic valvular disease with a murmur consistent with predominant aortic insufficiency, a pulse pressure of more than 90 mm. Hg, and x-ray and electrocardiographic evidence of left ventricular hypertrophy by the same criteria. The normal subjects were selected from personnel at Airborne Instruments Laboratory; the abnormal subjects were obtained through Memorial Hospital, New York City. Lead $V_5$ was obtained in the prone position from all subjects. It was recorded at a paper speed of 2 inches per second and a sensitivity of 2 inches per millivolt. The paper speed and sensitivity were selected to facilitate manual measurements. Instrumentation adequate to record tracings of these specifications was selected.*

Twelve electrocardiographic measurements were manually measured for each of five different heart cycles in each subject tested. All cycles were not at the same respiratory phase. The resulting differences are important but, since they are not usually considered in studies dealing with electrocardiographic measurements, they were not calculated.

A reference line was drawn through the electrocardiogram continuous with the P-Q segment. All amplitudes were manually measured as the maximum excursion from that reference line. All durations were measured as the time between the departure from and return to the reference baseline. When a particular wave did not return to the baseline, the change in slope at the beginning or at the end of the wave was used as the reference point of measurement. The exception to this rule was the measurement of the leading edge of the QRS, which was measured from the start of the Q wave to the peak of the R wave. "Segments" were measured from the end of one wave to the beginning of the following wave. The durations measured were those of the P, QR, QRS, and T waves, the P-R, (P-Q), and the Q-T segments. The amplitudes measured were those of the P, Q, R, S, and T waves and the S-T segment. The resulting measurements were entered on punch cards to permit

From the Heart Disease Control Program, Division of Chronic Diseases, Public Health Service, U. S. Department of Health, Education, and Welfare, Washington, D. C., and the Department of Medical and Biological Physics, Airborne Instruments Laboratory Inc., Deer Park, New York.

*A Visicorder, Model 906A, Minneapolis Minnesota, with preamplifiers and amplifiers built by Airborne Instrument Laboratory, Deer Park, Long Island, New York, were used.

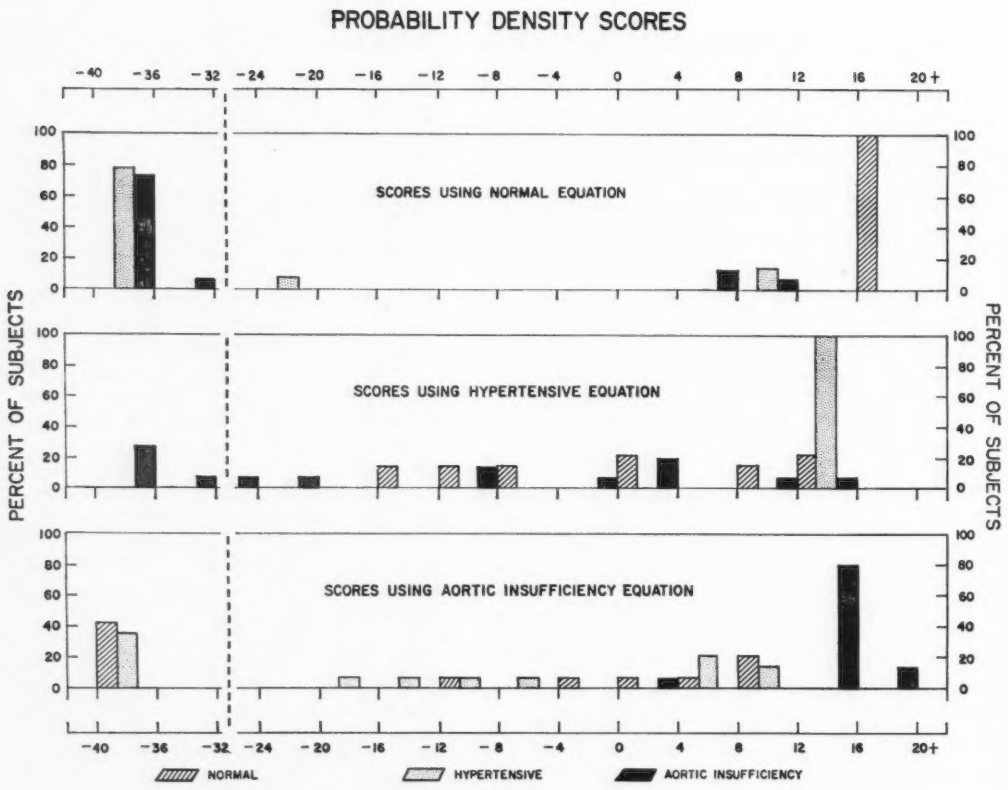


**Figure 1**

*Actual scores for each person are listed in table 4. In this figure the scores were arrayed according to their power of 10 for simplicity. This is sufficient to illustrate the separability that can be effected by probability density functions.*

**Table 1**

*Means and Variances for Electrocardiogram Variables*

| Data Points | Units | Normal Means | Normal Variance | Hypertensive Means | Hypertensive Variance | Aortic insufficiency Means | Aortic insufficiency Variance |
|---|---|---|---|---|---|---|---|
| $P_a$* | mv. | 0.06 | .00016 | 0.08 | .00057 | 0.07 | .00066 |
| $Q_a$ | mv. | −0.06 | .00290 | −0.06 | .00390 | −0.18 | .01950 |
| $R_a$ | mv. | 0.82 | .05830 | 1.99 | .32000 | 2.01 | .28900 |
| $S_a$ | mv. | −0.16 | .02310 | −0.26 | .02660 | −0.09 | .02040 |
| $T_a$ | mv. | 0.27 | .00091 | −0.06 | .19000 | 0.14 | .06760 |
| $ST_a$ | mv. | 0.06 | .00070 | −0.10 | .02280 | −0.04 | .01080 |
| $P_d$ | sec. | 0.11 | .00010 | 0.12 | .00021 | 0.11 | .00022 |
| $QRS_d$ | sec. | 0.09 | .00013 | 0.10 | .00028 | 0.09 | .00027 |
| $QR_d$ | sec. | 0.04 | .00008 | 0.05 | .00007 | 0.05 | .00007 |
| $T_d$ | sec. | 0.17 | .00019 | 0.19 | .00121 | 0.16 | .00260 |
| $PR_s$ | sec. | 0.04 | .00031 | 0.06 | .00034 | 0.06 | .00077 |
| $QT_s$ | sec. | 0.20 | .00055 | 0.21 | .00075 | 0.25 | .00110 |

*Small letters after designations for electrocardiographic wave forms stand for amplitude (a), duration (d), and segment (s). Units were measured in millivolts (mv.) and seconds (sec.).

**Table 2A**

*Correlation Coefficients for Normal Subjects*

| Data pts. | $P_a$ | $Q_a$ | $R_a$ | $S_a$ | $T_a$ | $ST_a$ | $P_d$ | $QRS_d$ | $QR_d$ | $T_d$ | $PR_s$ | $QT_s$ |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| $P_a$ | | −.282 | .022 | .106 | .258 | .349 | .149 | .222 | .222 | .193 | −.088 | −.175 |
| $Q_a$ | | | −.815 | −.336 | −.532 | −.433 | −.524 | −.280 | −.433 | −.362 | .207 | .349 |
| $R_a$ | | | | .413 | .547 | .405 | .545 | .139 | .153 | .026 | −.101 | .122 |
| $S_a$ | | | | | .153 | −.441 | .513 | −.319 | −.036 | .412 | −.044 | .467 |
| $T_a$ | | | | | | .595 | .427 | .382 | .574 | .111 | −.272 | .084 |
| $ST_a$ | | | | | | | −.006 | .618 | .239 | −.181 | −.152 | −.278 |
| $P_d$ | | | | | | | | −.115 | .186 | .481 | −.378 | .615 |
| $QRS_d$ | | | | | | | | | .419 | −.048 | .064 | .040 |
| $QR_d$ | | | | | | | | | | .313 | −.161 | .398 |
| $T_d$ | | | | | | | | | | | .092 | .537 |
| $PR_s$ | | | | | | | | | | | | −.038 |

**Table 2B**

*Correlation Coefficients for Hypertensive Subjects*

| Data pts. | $P_a$ | $Q_a$ | $R_a$ | $S_a$ | $T_a$ | $ST_a$ | $P_d$ | $QRS_d$ | $QR_d$ | $T_d$ | $PR_s$ | $QT_s$ |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| $P_a$ | | .004 | −.031 | −.033 | −.131 | .157 | .110 | −.335 | −.345 | −.645 | −.163 | −.425 |
| $Q_a$ | | | −.249 | −.233 | −.292 | −.384 | .197 | −.074 | −.234 | −.069 | .274 | .103 |
| $R_a$ | | | | −.126 | −.012 | −.131 | .396 | .291 | .104 | .074 | −.066 | .206 |
| $S_a$ | | | | | −.029 | .133 | −.411 | −.288 | .003 | −.284 | −.287 | .156 |
| $T_a$ | | | | | | .816 | −.263 | −.361 | −.177 | .329 | −.035 | .074 |
| $ST_a$ | | | | | | | −.119 | −.303 | −.126 | .007 | −.084 | −.047 |
| $P_d$ | | | | | | | | .506 | .296 | .159 | .013 | .166 |
| $QRS_d$ | | | | | | | | | .778 | .320 | −.233 | .380 |
| $QR_d$ | | | | | | | | | | .338 | −.371 | .678 |
| $T_d$ | | | | | | | | | | | −.024 | .501 |
| $PR_s$ | | | | | | | | | | | | .019 |

using the information in a general purpose computer. The average value of each of the measurements was determined and used in subsequent computations.

It was assumed that the distributions of variables in the electrocardiograms could be described by multivariate normal distribution curves. These are completely determined by the means and the variance (table 1) and the correlation coefficients (table 2) of each variable with every other variable. Thus, in the analysis made in this paper the means, variances, and correlation coefficients were used, in combination, as the best estimate of an electrocardiographic waveform or interval.

The statistical significance of the differences between the means, variances, and the correlation coefficients for the normal and pathologic groups was obtained. The means, variances, and correlation coefficients of the variables that had significant differences are listed in table 3. Those above the level of 99 per cent were used in combination for each group of subjects by the method of maximum likelihood[2] to obtain an array of values. The distribution of the array of value combinations shows their frequency of occurrence in the groups of subjects under study. The frequency of occurrence in the distribution has a relationship that can be defined by the probability density function, which was the basis of the statistical analysis used in this study. The equation for the probability density function was of the form given in Davenport and Root.[3]

Subsequent to the derivation of equations representative of normal and pathologic subjects as entire groups, the variables from each subject, previously included in one of the three groups, were used in each of the three equations and a value or score for each subject was obtained. The score determines each subject's position in the distribution.

The probability density function may be looked upon as a description of the characteristics of a given group against which any unknown subject can be tested. The score obtained by use of the

**Table 2C**

*Correlation Coefficients for Subjects with Aortic Insufficiency*

| Data pts. | $P_a$ | $Q_a$ | $R_a$ | $S_a$ | $T_a$ | $ST_a$ | $P_d$ | $QRS_d$ | $QR_d$ | $T_d$ | $PR_a$ | $QT_a$ |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| $P_a$ | | −.214 | .056 | .120 | .146 | .053 | .539 | .008 | −.168 | −.050 | −.122 | −.120 |
| $Q_a$ | | | −.645 | −.242 | .213 | −.204 | −.060 | −.505 | −.385 | .394 | −.280 | −.277 |
| $R_a$ | | | | .004 | −.116 | .158 | −.002 | .727 | .444 | −.312 | .629 | .357 |
| $S_a$ | | | | | −.566 | −.294 | .056 | −.189 | .123 | .032 | .090 | .176 |
| $T_a$ | | | | | | .562 | −.286 | .041 | −.531 | −.369 | −.363 | .106 |
| $ST_a$ | | | | | | | −.136 | −.255 | −.269 | −.324 | −.527 | .066 |
| $P_d$ | | | | | | | | .079 | −.197 | −.012 | .092 | −.621 |
| $QRS_d$ | | | | | | | | | .672 | −.050 | .644 | .202 |
| $QR_d$ | | | | | | | | | | .179 | .564 | .293 |
| $T_d$ | | | | | | | | | | | −.354 | −.301 |
| $PR_a$ | | | | | | | | | | | | .362 |

**Table 3A**

*Electrocardiographic Variables. The Level of Tests of Significance of the Difference of Means and Variances*

| Significance level | Hypertensive vs normal | | Aortic insufficiency vs normal | | Hypertensive vs aortic insufficiency | |
|---|---|---|---|---|---|---|
| | Means | Var. | Means | Var. | Means | Var. |
| 99% | $R_a$ | $R_a$ | $R_a$ | $R_a$ | $Q_a$ | $Q_a$ |
| | $ST_a$ | $ST_a$ | $ST_a$ | $ST_a$ | QT | $Q_a$ |
| | | $T_a$ | $QR_d$ | $T_a$ | $S_a$ | |
| | | $T_d$ | $Q_a$ | $P_a$ | | |
| | | $P_a$ | $QT_a$ | $Q_a$ | | |
| | | | | $T_d$ | | |
| 95% | $P_a$ | | | $P_d$ | | $T_a$ |
| | $T_a$ | | | $QRS_d$ | | |
| | $P_d$ | | | $PR_a$ | | |
| | | | | $QT_a$ | | |
| 90% | $T_d$ | $P_d$ | $T_a$ | | $P_d$ | $T_d$ |
| | $QR_d$ | $QRS_d$ | $P_d$ | | $QRS_d$ | $PR_d$ |
| | $PR_a$ | | $PR_a$ | | $T_d$ | $ST_a$ |

equation for probability density function results in an index of compatibility of the unknown subject to the group from which the equation was derived.

## Results

The scores derived from the probability density equations for each of 43 subjects are given in table 4.* The closer the score of a particular subject to that of the group under consideration, the more likely it is that the subject belongs to that particular group. By use of these scores a significant separation was obtained between normal and pathologic subjects. Separation of the subjects with left ventricular hypertrophy into categories of hypertension and aortic insufficiency was also possible, although the degree of separation was not so great (fig. 1). Although the ranges of the scores overlap among pathologic groups, use of a subject's variables successively in each equation allows adequate separation in each individual case.

All the selected electrocardiographic measurements played a part in the group separations, since each variable had either a mean, variance, or one correlation coefficient that showed significant differences from one of the

*Because of an error in transcribing the variables for subjects 3 and 25, the values of their probability density functions are always zero. These subjects were dropped from further analysis.

**Table 3B**

*Significant Correlation Coefficients*

| Significance level | Normal vs hypertension | | Normal vs aortic insufficiency | | Hypertension vs aortic insufficiency | |
|---|---|---|---|---|---|---|
| 99% | $P_s$ | $T_d$ | $Q_s$ | $T_s$ | $P_s$ | $T_d$ |
| | $Q_s$ | $P_d$ | $Q_s$ | $T_d$ | $R_s$ | $PR_s$ |
| | $S_s$ | $P_d$ | $R_s$ | $T_s$ | $T_s$ | $T_d$ |
| | $S_s$ | $T_d$ | $R_s$ | $QRS_d$ | $P_d$ | $QT_s$ |
| | $T_s$ | $QRS_d$ | $R_s$ | $T_d$ | $QRS_d$ | $PR_s$ |
| | $ST_s$ | $QRS_d$ | $R_s$ | $PR_s$ | $QR_d$ | $PR_s$ |
| | $Q_s$ | $R_s$ | $S_s$ | $QR_d$ | $T_d$ | $QT_s$ |
| | | | $T_s$ | $P_d$ | | |
| | $T_s$ | $QR_d$ | $T_s$ | $QR_d$ | | |
| | $R_s$ | $T_s$ | $T_s$ | $ST_s$ | | |
| | $T_s$ | $P_d$ | $ST_s$ | $QRS_d$ | | |
| | $P_d$ | $QRS_d$ | $P_d$ | $QRS_d$ | | |
| | | | $P_d$ | $QT_s$ | | |
| | | | $R_s$ | $P_d$ | | |
| | | | $S_s$ | $P_d$ | | |
| | | | $ST_s$ | $P_d$ | | |
| | | | $T_d$ | $PR_s$ | | |
| | | | $T_d$ | $QT_s$ | | |
| 95% | $P_s$ | $QRS_d$ | $P_s$ | $P_d$ | $P_s$ | $P_d$ |
| | $P_s$ | $QR_d$ | $Q_s$ | $P_d$ | $Q_s$ | $R_s$ |
| | $Q_s$ | $QT_s$ | $Q_s$ | $PR_s$ | $Q_s$ | $T_s$ |
| | $R_s$ | $S_s$ | $R_s$ | $ST_s$ | $Q_s$ | $QRS_d$ |
| | $R_s$ | $ST_s$ | $T_s$ | $QT_s$ | $Q_s$ | $T_d$ |
| | $S_s$ | $ST_s$ | $P_d$ | $QR_d$ | $Q_s$ | $PR_s$ |
| | $T_s$ | $ST_s$ | $P_d$ | $T_d$ | $S_s$ | $P_d$ |
| | $P_d$ | $QT_s$ | $QRS_d$ | $QR_d$ | $T_s$ | $ST_s$ |
| | $QRS_d$ | $QR_d$ | | | $ST_s$ | $PR_s$ |
| | | | | | $P_d$ | $QRS_d$ |
| | | | | | $P_d$ | $QR_d$ |
| | | | | | $QR_d$ | $QT_s$ |
| 90% | $P_s$ | $R_s$ | $P_s$ | $QR_d$ | $P_s$ | $QRS_d$ |
| | $P_s$ | $T_s$ | $Q_s$ | $R_s$ | $Q_s$ | $QT_s$ |
| | $R_s$ | $T_d$ | $R_s$ | $S_s$ | $R_s$ | $P_d$ |
| | $ST_s$ | $QR_d$ | $ST_s$ | $T_d$ | $R_s$ | $QR_d$ |
| | $P_d$ | $T_d$ | $QRS_d$ | $QT_s$ | $R_s$ | $T_d$ |
| | $P_d$ | $PR_s$ | | | $S_s$ | $ST_s$ |
| | $QRS_d$ | $T_d$ | $QR_d$ | $QT_s$ | $S_s$ | $PR_s$ |
| | $QRS_d$ | $QT_s$ | | | $S_s$ | $QT_s$ |
| | $QR_d$ | $QT_s$ | | | $T_s$ | $QRS_d$ |
| | | | | | $T_s$ | $QR_d$ |
| | | | | | $QRS_d$ | $T_d$ |
| | | | | | $PR_s$ | $QT_s$ |

groups to another at the 99-per cent level. Some correlation coefficients were significant at the 99-per cent level when neither the mean nor the variance of the variables approximated that level. This implies that although certain variables do not seem to aid separating normal from abnormal subjects, their joint interaction is significant.

## Discussion

No attempt was made to determine the weight of each electrocardiographic variable in achieving separation. Such determinations will be of importance in future attempts to reduce the quantity of input data required for group differentiation. Although the usefulness of electrocardiographic variables for

**Table 4**

*Probability Density Scores Based on Electrocardiographic Variables*

| | Subject | Normal | Hypertensive | Aortic insufficiency |
|---|---|---|---|---|
| Normal | 1 | 0.2961 (17) | 0.3603 (03) | * |
| | 2 | 0.2871 (17) | 0.6213 (11) | * |
| | 3 | .... | .... | .... |
| | 4 | 0.3001 (18) | 0.4549 (−04) | 0.3693 (−08) |
| | 5 | 0.1349 (18) | 0.1129 (10) | 0.7577 (−37) |
| | 6 | 0.3406 (18) | 0.3245 (01) | * |
| | 7 | 0.6772 (17) | 0.1160 (14) | 0.2303 (09) |
| | 8 | 0.8284 (17) | 0.7488 (00) | 0.9243 (03) |
| | 9 | 0.7648 (17) | 0.7697 (−15) | * |
| | 10 | 0.5519 (17) | 0.5809 (−04) | 0.3704 (05) |
| | 11 | 0.8398 (18) | 0.5680 (−11) | 0.1794 (−01) |
| | 12 | 0.5685 (18) | 0.2548 (−09) | 0.7230 (−16) |
| | 13 | 0.9914 (18) | 0.8912 (14) | * |
| | 14 | 0.2293 (18) | 0.1226 (−15) | 0.2549 (09) |
| | 15 | 0.5330 (17) | 0.1951 (12) | 0.1715 (08) |
| Hypertensive | 16 | * | 0.2045 (15) | 0.3782 (07) |
| | 17 | * | 0.2785 (15) | * |
| | 18 | * | 0.6277 (15) | 0.1084 (−12) |
| | 19 | * | 0.1206 (15) | * |
| | 20 | * | 0.3536 (15) | 0.3897 (−15) |
| | 21 | * | 0.1622 (15) | 0.3532 (06) |
| | 22 | 0.1528 (−20) | 0.3254 (15) | 0.3862 (08) |
| | 23 | 0.8675 (09) | 0.9782 (15) | 0.1531 (09) |
| | 24 | * | 0.7155 (15) | 0.2697 (04) |
| | 25 | .... | .... | .... |
| | 26 | * | 0.6173 (15) | 0.9454 (−19) |
| | 27 | * | 0.1233 (15) | * |
| | 28 | 0.3433 (10) | 0.5219 (15) | * |
| | 29 | * | 0.1381 (15) | * |
| | 30 | * | 0.2277 (15) | 0.9823 (−09) |
| Aortic insufficiency | 31 | 0.2297 (−32) | 0.1598 (−01) | 0.4116 (15) |
| | 32 | 0.4413 (05) | 0.2614 (01) | 0.8787 (15) |
| | 33 | * | * | 0.2094 (15) |
| | 34 | * | * | 0.1347 (15) |
| | 35 | * | 0.5374 (−35) | 0.1235 (15) |
| | 36 | * | * | 0.1674 (02) |
| | 37 | 0.2176 (11) | 0.4116 (−25) | 0.1646 (15) |
| | 38 | * | 0.2769 (−10) | 0.1510 (15) |
| | 39 | * | 0.6610 (03) | 0.2039 (15) |
| | 40 | 0.8333 (06) | 0.4342 (03) | 0.1355 (16) |
| | 41 | * | * | 0.1279 (15) |
| | 42 | * | 0.7416 (09) | 0.1584 (16) |
| | 43 | * | 0.4822 (−21) | 0.7795 (15) |
| | 44 | * | 0.3203 (−11) | 0.1228 (15) |
| | 45 | * | 0.1679 (12) | 0.6784 (15) |

*Less than $10^{-38}$

Note: The number in parentheses indicates the power of 10 with which the preceding number must be multiplied.

statistical differentiation does not imply that they have physiologic relationships, statistically significant differences among them suggest areas for possible fruitful physiologic studies in the future.

This study used probability density functions as its statistical basis. That method was selected because of availability of personnel knowledgeable in its applications and programming. Success in its use emphasizes that it and numerous other methods of analysis applicable to computers[5] are available as medical tools.

As would be expected, the analysis of a single lead of an electrocardiogram was sufficient to effect a separation between the normal and abnormal groups because of initial preselection on the basis of marked difference between groups. The subjects of this study were highly preselected, in order to obtain equations that would be characteristic for a well-defined group. It is expected that an overlap in distribution of scores derived from these equations will exist in the usual clinical distribution of subjects. The advantage of the technic is that the analyzed values, including "borderline" ones can be quantitated to give the physician a means of adding a definitive weight to his consideration of the electrocardiogram in his clinical diagnosis.

Although more information may be available in the electrocardiographic curve, as much as is currently useful clinically, or perhaps more, was derived from the 12 variables selected for this study. The electrocardiographic measurements used in this study were of some significance in differentiation; this does not imply that an entirely different set would not have done equally well but rather suggests that other sets and attempts to reduce the quantity of input data requires trial. The electrocardiographic separation was based on criteria of duration and amplitude without consideration of slope or "pattern" of waves. This suggests, as do extensive studies based on normal individuals,[6-8] that numerical analysis of electrocardiographic waves can be used to form the basis for standardization of electrocardiographic interpretation.

Many applications of these technics to clinical practice and methods of handling medical data can be envisioned. The methods of analysis of electrocardiographic variables in this study offer technics particularly useful for analysis of data from large groups of subjects. These technics thus offer possibilities for advancement of methods used in clinical diagnosis, epidemiologic studies, and the tabulation and processing of medical data.

### Summary and Conclusions

Electrocardiography is particularly suitable for computer analysis because of the availability of quantitative objective data in that field. With use of this technic, this study demonstrates that electrocardiographic measurements from a single standard lead were sufficient to separate the electrocardiograms into groups that can be related to clinical characteristics. Medical applications of these technics are suggested.

### Acknowledgment

Appreciation is expressed to Mr. Mort Gilbert, of the Information Office of the Heart Disease Program, for his review and assistance.

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# A Nomogram for Long-Term Anticoagulant Therapy

*By* WILLIAM R. TENCH, M.D., AND HUGH C. ROSS, B.S.

THE ROUTINE USE of anticoagulants on an ambulant basis is modified by many variables. Among these are bleeding tendencies, renal and hepatic disease preexisting or developing during such therapy, and complications of the primary disease. Increased sensitivity to anticoagulants enhanced by minor alcohol excesses and other medications may be further imbalanced by memory defects or excessive compulsions. These variables are carefully weighed in the decision to initiate this therapy. But even in their absence the problem of recommending predictable dose schedules tends to be resolved by the trial and error of experience. Physicians who are not primarily interested in this therapy tend to shy away often when it is sorely indicated. The purpose of this report is to present a means for the management of long-term anticoagulant therapy.

The basis for this presentation has been the management of 278 patients comprising 470 patient-years. Their course and complications are not the subject of this report. From this experience, however, a nomogram has been derived to improve the ease and efficiency of long-term anticoagulant therapy. About 200 patients initially given Dicumarol have been retained on this anticoagulant. During the past 2 years additional patients have been given Warfarin sodium. Currently of 242 patients, 158 are taking Dicumarol. The remaining 84 are on Warfarin sodium. There appears to be no significant difference in the effectiveness of either anticoagulant other than a 10:1 ratio of the former over the latter for maintenance purposes. Values in the nomogram are multiplied by 10 for patients on Dicumarol. Prothrombin times have been performed by the one-stage Quick method by use of a 13-second control thromboplastin (Simplastin). When carefully performed, the reliability of this test may be indicated by the following:

1. Twenty determinations on the same normal person yielded prothrombin times from 13.7 to 14.5 seconds, with a mean value of 14.09 seconds. Standard deviation of the mean, ± 0.22 second.

2. Ten determinations on a commercial plasma (Diagnostic Plasma, Warner-Chilcott) yielded prothrombin times from 13.8 to 14.2 seconds, with a mean value of 14.03 seconds. Standard deviation of the mean, ± 0.10 second.

3. Ten determinations on a second test plasma (Standardized Normal Plasma, Dade Reagents, Inc.) yielded prothrombin times from 12.9 to 13.5 seconds, with a mean value of 13.24 seconds. Standard deviation of the mean ± 0.23 second. Initially the primary objective was to establish a patient's specific weekly requirement for the anticoagulant. This varied from 10 mg. of Warfarin weekly, and schedules were drawn progressively, increasing by small increments to 220 mg. weekly as may be seen centered in the nomogram (fig. 1). Almost a third of these patients required less than 30 mg. weekly. Therefore to avoid early difficulties 25 mg. of Warfarin sodium are used initially in practically all patients. Five milligrams are given the second day, and a prothrombin time is performed on the third day, acutely ill patients being "covered" with heparin. The degree of sensitivity to the anticoagulant, as reflected by the first prothrombin time, has been used to indicate the approximate daily dose. Subsequent prothrombin times serve to place a patient in his particular weekly dose schedule. The schedules themselves are patterned to make it easy to memorize them.

Two years ago a chart was constructed with the left-hand vertical column representing increasing weekly doses. Opposite each weekly

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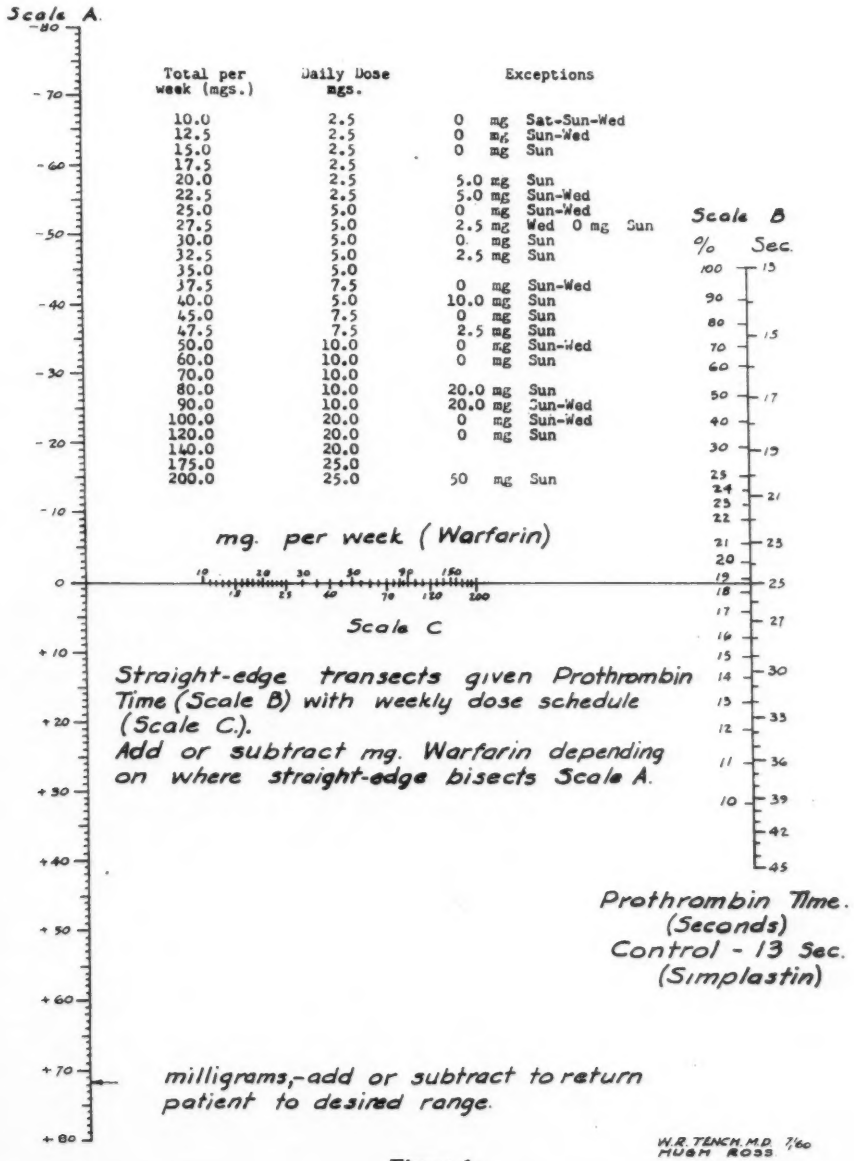


**Figure 1**

*The nomogram itself.*

schedule, ascending from 13 seconds to 50 seconds, were the milligrams of Warfarin required or omitted to return a given schedule to its desirable range (table 1). The original adjustments for the chart, depicted in table 1, were entirely arbitrary, modified at frequent intervals through the experience of trial and error. As more and more points were obtained yielding a satisfactory response to a given adjustment for a specific weekly dose schedule, the predictability of the chart improved. It was then noted that these incre-

## Table 1

*An Abbreviation of the Chart Used for the Management of Long-Term Anticoagulant Therapy for a Two-Year Period and from Which the Nomogram Was Constructed*

| P.T. in Seconds | Warfarin Sodium—mgs., per week | Mgs. added | | | | ← | | | | → | | | | | Days omitted (Mgs. subtracted from week's usual dose) | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 | 21 | 22 | 23 | 24 | 25 | 26 | 27 | 28 | 29 | 30 | 31 | 32 | 33 | 34 | 35 | |
| 10 | 10 | 10 | 7.5 | 7.5 | 5 | 5 | 5 | 5 | x | x | x | x | x | 1 | 1 | 2 | 2 | 2 | 3 | 3 | 3 | 3 | 4 | days |
| | | | | | | | | | | | | | | (1.4 | 1.4 | 2.8 | 2.8 | 2.8 | 4.3 | 4.3 | 4.3 | 4.3 | 5.7) | mg. |
| 15 | 12.5 | 10 | 7.5 | 7.5 | 5 | 5 | 5 | 5 | x | x | x | x | x | 1 | 1 | 2 | 2 | 2 | 3 | 3 | 3 | 3 | 4 | days |
| | | | | | | | | | | | | | | (2.2 | 2.2 | 3.6 | 3.6 | 3.6 | 5.4 | 5.4 | 5.4 | 5.4 | 7.2) | mg. |
| 20 | 15 | 15 | 12.5 | 10 | 10 | 75 | 75 | 75 | 5 | x | x | x | x | 1 | 1 | 1.5 | 1.5 | 2 | 2 | 2 | 3 | 3 | 3 | days |
| | | | | | | | | | | | | | | (2.8 | 2.8 | 4.3 | 4.3 | 5.7 | 5.7 | 5.7 | 8.6 | 8.6 | 8.6) | mg. |
| 25 | 20 | 20 | 15 | 12.5 | 12.5 | 10 | 10 | 75 | 75 | 5 | x | x | x | 0.5 | 0.5 | 1 | 1 | 1.5 | 2 | 2 | 2 | 2 | 3 | days |
| | | | | | | | | | | | | | | (1.8 | 1.8 | 3.6 | 3.6 | 5.4 | 7.2 | 7.2 | 7.2 | 7.2 | 10.8) | mg. |
| 30 | 20 | 20 | 17.5 | 15 | 15 | 12.5 | 10 | 10 | 75 | 5 | x | x | x | 0.5 | 0.5 | 0.5 | 1 | 1 | 1.5 | 1.5 | 2 | 2 | 2 | days |
| | | | | | | | | | | | | | | (2.2 | 2.2 | 2.2 | 4.3 | 4.3 | 6.5 | 6.5 | 8.6 | 8.6 | 8.6) | mg. |
| 35 | 25 | 20 | 20 | 17.5 | 15 | 12.5 | 12.5 | 10 | 10 | x | x | x | x | 0.5 | 0.5 | 0.5 | 1 | 1 | 1.5 | 1.5 | 1.5 | 2 | 2 | days |
| | | | | | | | | | | | | | | (2.5 | 2.5 | 2.5 | 5.0 | 5.0 | 7.5 | 7.5 | 7.5 | 10 | 10 ) | mg. |
| 40 | 30 | 20 | 20 | 20 | 17.5 | 15 | 15 | 12.5 | 10 | 75 | x | x | x | 0.5 | 0.5 | 1 | 1 | 1 | 1.5 | 1.5 | 2 | 2 | 2.5 | days |
| | | | | | | | | | | | | | | (2.8 | 2.8 | 5.7 | 5.7 | 5.7 | 8.6 | 8.6 | 11.4 | 11.4 | 14.3) | mg. |
| 45 | 30 | 20 | 20 | 20 | 17.5 | 17.5 | 15 | 12.5 | 10 | 75 | x | x | x | 0.5 | 0.5 | 0.5 | 1 | 1 | 1 | 1.5 | 1.5 | 2 | 2 | days |
| | | | | | | | | | | | | | | (3.2 | 3.2 | 3.2 | 6.4 | 6.4 | 6.4 | 9.6 | 9.6 | 12.8 | 12.8) | mg. |
| 50 | 35 | 30 | 25 | 20 | 20 | 17.5 | 17.5 | 15 | 10 | x | x | x | x | 0.5 | 0.5 | 0.5 | 1 | 1 | 1 | 1.5 | 1.5 | 2 | 2 | days |
| | | | | | | | | | | | | | | (3.6 | 3.6 | 3.6 | 7.2 | 7.2 | 7.2 | 10.8 | 10.8 | 14.4 | 14.4) | mg. |
| 80 | 50 | 40 | 35 | 25 | 25 | 20 | 17.5 | 17.5 | 15 | 15 | 12.5 | x | x | | | 0.5 | 0.5 | 0.5 | 1 | 1 | 1 | 1 | 1.5 | days |
| | | | | | | | | | | | | | | | | (5.7 | 5.7 | 5.7 | 11.4 | 11.4 | 11.4 | 11.4 | 17.1) | mg. |
| 100 | 60 | 50 | 40 | 35 | 30 | 25 | 25 | 20 | x | x | x | x | x | | | | 0.5 | 0.5 | 0.5 | 0.5 | 1 | 1 | 1 | days |
| | | | | | | | | | | | | | | | | | (7.2 | 7.2 | 7.2 | 7.2 | 14.4 | 14.4 | 14.4) | mg. |

Opposite the patients usual weekly requirement of Warfarin is chosen the adjustment required beneath a given prothrombin time.
X = No change in schedule.
The right half of this chart is interpreted in days of omission of usual dose. Half days equal one half a given days dose.
In parenthesis would be milligrams corresponding to such omissions—values employed in drawing the curves in Figure 2.

**Table 2**

*Summary of Progressive Improvement in Managing Patient without the Chart, with the Chart, and Finally with the Nomogram*

| Case | N | $\sqrt{n}$ | S | $\frac{1.96 \cdot S}{\sqrt{n}}$ | $\bar{X} \pm$ Tolerance |
|---|---|---|---|---|---|
| Seconds deviation in desired prothrombin time per number | | | | | |
| No chart | 36 | 6 | 2.68 | .875 | 7.75 ± .875 |
| Chart | 36 | 6 | 1.96 | .640 | 5.4 ± .640 |
| Nomogram | 32 | 5.65 | 0.93 | .318 | 1.90 ± .318 |
| Nomogram | 97 | 9.4 | 2.24 | .467 | 2.3 ± .467 |
| Number corrections in dosage required per year | | | | | |
| No chart | 36 | 6 | 4.3 | 1.41 | 18.3 ± 1.41 |
| Chart | 36 | 6 | 4.14 | 1.36 | 15.3 ± 1.36 |
| Nomogram | 32 | 5.65 | 4.86 | 1.69 | 7.2 ± 1.5 |
| Nomogram | 97 | 9.4 | 1.50 | .945 | 8.4 ± .945 |

ments or omissions followed a pattern. Curves were then drawn by plotting on the abscissa the number of milligrams required to return a patient to the desired range against the ordinate, representing the prothrombin time in seconds with progressively greater weekly doses required (fig. 2). These curves were found to follow a linear pattern when plotted on semilog paper and to conform to the equation $\triangle D = 8.95\ DN\ .62 \log \frac{25}{t}$. $\triangle D$ represents the adjustment necessary to return a patient to a satisfactory level and DN represents his weekly dose. As may be seen in figure 2, by adapting "the best straight line" to these curves, shortcomings in the ranges of 20 to 25 seconds (23 to 18 per cent) could be corrected. Now, either a new, more accurate chart could be composed or a more versatile instrument, such as a nomogram, could be constructed (fig. 1) with three variables.* 1. Prothrombin time in seconds (or per cent). 2. Individual dose schedule per week. 3. Varying dose schedules of the anticoagulant per patient.

A straight edge is laid from a point on the right hand vertical scale (scale B) which is determined by a prothrombin time done on the patient's usual test day. When laid across the horizontal line (scale C) at a point correspondng to his usual weekly requirement of the anticoagulant, it transects the left-hand vertical line (scale A) at a point where one may read off the number of milligrams necessary to add or subtract from his current week's dosage to restore him to the desired 24-second level on his subsequent test date, 2 to 4 weeks hence.

For example, a patient taking 50 mg. of Warfarin sodium per week, i.e., 10 mg. daily omitting Sunday and Wednesday, is found on his test day to have a prothrombin time 17 seconds. The straight edge is placed at 17 seconds on scale B and when laid across scale C at 50 mg. it is found to transect scale A at +17.5 mg. One therefore advises him to take 3½ of the 5-mg. tablets extra "today" and then to continue his usual schedule and return in 2 weeks or whatever period he has been found to require for readjustment. If his prothrombin time is 35 seconds, the straight edge is found to transect scale A at −15 mg., which would result in the advice to omit "today's" Warfarin entirely and to take only 5 mg. "tomorrow." If "tomorrow" or "today" were a "skip day," he is advised to carry out the same omissions the following days. If a prothrombin time is found to be over 45 seconds (less than 9 per cent), 5 or 10 mg. of vitamin $K_1$ oxide (Mephyton) are advised, prothrombin times are done at shorter intervals, and other reasons for instability are sought. Should he consistently require either

*See appendix for construction of nomogram.

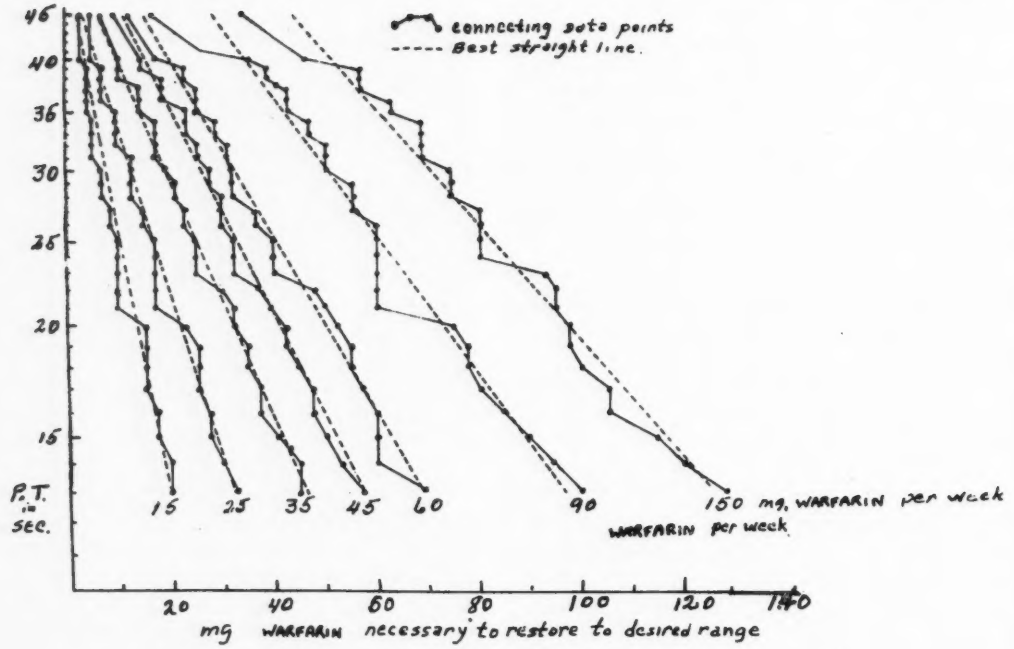


**Figure 2**

*An abbreviation of curves based on table 1 and their major points connected to reveal the relationship of increasing weekly dosage (DN); the required change in dose (△ D); and the measured prothrombin time (P.T.).*

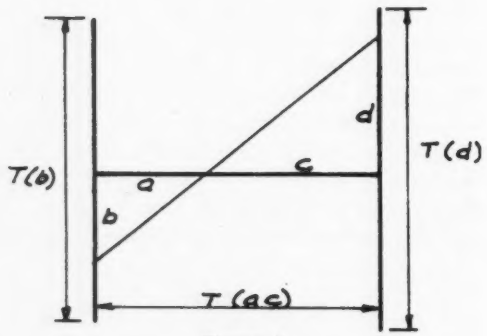


**Figure 3**

*Mathematical expression of construction of nomogram.*

subtraction or addition of his usual dose, he is changed to a larger or smaller weekly dose schedule.

The ideal record of a patient on this therapy would reveal that in 1 year a prothrombin time every 2 weeks or 26 times in the year would not require a single adjustment, and that at no time would it vary from 24 to 30 seconds, if the thromboplastin used were controlled at 13 seconds. Thirty-six patients were found to have been observed continuously for 3 years. One year before the chart was constructed from which the nomogram is derived their records were analyzed to determine the frequency and degree that they varied from such an ideal record. Their records were again compared to a 1-year period when their management was controlled by the chart itself. To 32 (the sequence having been interrupted in four) of these same patients were added 65; they were all controlled by the nomogram alone for a 6-month period. In the management of the first group it was found that 36 patients required 659 readjustments and fell short by a total of 2,789 seconds. Each patient averaged 7.75 seconds per month below

the desired 24-second level, with a standard deviation of 2.7 second, and required an average of 18 adjustments a year, with a standard deviation of 4.3. With the aid of the chart, they required 550 readjustments but still fell short 1,952 seconds. Each patient now averaged 5.4 seconds per month, with a standard deviation of 1.96, and required 15.3 readjustments in the year, with a standard deviation of 4.14.

Under control by the nomogram, these same patients averaged 1.95 seconds low per month, with a standard deviation of 0.93, and required readjustments at a rate of only 7.2 per year, with a standard deviation of 4.86. When the additional 65 patients were incorporated within the last group, the average time a patient fell short became 2.3 seconds per month, with a standard deviation of 2.24, and required 8.4 adjustments, with a standard deviation of 1.5 for the year. As may be seen in table 2, employing the formula $\frac{1.96 \cdot s}{\sqrt{n}}$ the improvement has been significant.

"If we take a random sample of size 'n,' where N is 30 or more, and calculate $\overline{X}$ and s of this sample, then we can assert with a probability of about .95 that $\overline{X}$ will not differ from the true mean of the population by more than $\frac{1.96 \cdot s}{\sqrt{n}}$ ."[1]

## Summary

It appears that the nomogram, because of its predictability, has been useful, not only in patients who tend to vary their requirements, but as a tool to find the proper weekly schedule for each patient. Moreover, prothrombin times have tended to lose their peaks and valleys; adjustments have become less frequent and of much smaller degree.

## Conclusion

Experience in long-term anticoagulant therapy has served as a basis for the development of a nomogram for its management.

## Reference

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## Appendix

### Determination of Equation of Basic Data

The basic data consisting of measured prothrombin time (P.T.) vs. required change in dose ($\Delta D$) to return a patient to the desired prothrombin time of 25 seconds was plotted on semilog paper (t on log scale).

A separate straight-line plot of increasing slope for increasing weekly dosage (DN) was obtained for each increment of Dn indicating the relationship

$$\Delta D = F\,(DN) \log \frac{25}{t}$$

F (Dn) was then plotted vs. Dn on log-log paper. A straight line function was obtained of the equation $F\,(Dn) = 8.95\,(Dn)^{\cdot 62}$.

Combining the above two equations, all of the information contained in the basic data can be expressed by the equation:

$$\Delta D = 8.95\,DN^{\cdot 62} \log \frac{25}{t}$$

### Construction of Nomogram

A nomogram was constructed to provide a simple method for solving the equation:

$$\Delta D = 8.95\,(DN)^{\cdot 62} \log \frac{25}{t} \qquad (1)$$

The design of the nomogram was based on the geometry of figure 3 which yields the identity:

$$b = \frac{a}{c}\, d \qquad (2)$$

Equating like parts of (1) and (2) yields:

$$b = \Delta D,\ \frac{a}{c} = 8.95\,(DN)^{\cdot 62},\ d = \log \frac{25}{t} \qquad (3)$$

Assuming that the same number of units per inch is used for each of the parameters in (3), then the equations are solved for the values of $\Delta D$, DN, and t and plotted to the chosen scale. In this equation the result was that either scale b was too long or d too short. This was compensated for as follows: if T (b) is the total length available for line b, and S ($\Delta D$) is the maximum value of $\Delta D$ minus the minimum value, then let $N_1 = T\,(b)/S\,(\Delta D)$. Similarly, let $N_2 = T\,(d)/S\,(\log \frac{25}{t})$.

Multiplying both sides of (2) by $N_1/N_2$:

$$\frac{Nb}{N_2} = \frac{N_1 a}{N_2 c}\, d$$

$$b\,N_1 = \frac{aN_1}{cN_2}\, dN_2 \qquad (4)$$

Equating (4) to (1):

$$b = \frac{\Delta D}{N_1} \qquad (5)$$

$$d = \frac{\log \frac{25}{t}}{N_2} \qquad (6)$$

$$a = c\,\frac{N_2}{N_1}\,8.95\,(DN)^{\cdot 62} \qquad (7)$$

In (7), if T (ac) is the total length available for line a + c, then c = T (ac) − a. Inserting this in (7):

$$a = \left[ T\,(ac) - a \right] \frac{N_2}{N_1}\, 8.95\,(DN)\,{}^{\bullet 62}$$

$$a \left[ \frac{N_1}{N_2} + 8.95\,(DN)\,{}^{\bullet 62} \right] = T\,(ac)\, 8.95\,(DN)\,{}^{\bullet 62}$$

$$a = \frac{T\,(ac)\, 8.95\,(DN)\,{}^{\bullet 62}}{\frac{N_1}{N_2} + 8.95\,(DN)\,{}^{\bullet 62}} \qquad (8)$$

(5), (6), and (8) are then solved for the values of ΔD t, and DN. These quantities are then plotted on the specified, b, d, or (ac) lines with the value of ΔD, t, or DN used to calculate a particular point noted next to that point. If T (b), T (d), and T (ac) are in inches, then $N_1$ and $N_2$ will be in units/inch and a, b, and d will be in inches.

## The Internal Environment

Ancient science was able to conceive only the outer environment; but to establish the science of experimental biology, we must also conceive an inner environment. I believe I was the first to express this idea clearly and to insist on it, the better to explain the application of experimentation to living beings. Since the outer environment, on the other hand, infiltrates into the inner environment, knowing the latter teaches us the former's every influence. Only by passing into the inner, can the influence of the outer environment reach us, whence it follows that knowing the outer environment cannot teach us the actions born in, and proper to, the inner environment. The general cosmic environment is common to living and to inorganic bodies; but the inner environment created by an organism is special to each living being. Now, here is the true physiological environment; this it is which physiologists and physicians should study and know, for by its means they can act on the histological units which are the only effective agents in vital phenomena.—CLAUDE BERNARD. *An Introduction to the Study of Experimental Medicine.* New York, The MacMillan Company, 1927, p. 76.

# Complete Atrioventricular Block due to Cardiac Metastasis of Bronchogenic Carcinoma

*By* GERALD D. BUCKBERG, B.S., AND NOBLE O. FOWLER, M.D.

ALTHOUGH cardiac arrhythmias are a common clinical manifestation of metastatic cardiac tumor, complete heart block is still a rather infrequent finding. The first reported example of complete atrioventricular block associated with metastatic carcinoma was made by Rosles in 1924.[1] The diagnosis was suspected clinically and confirmed at necropsy. In 1931, Yater[2] made the following statement concerning heart block, particularly when complete, "Any case of arrhythmia in which no satisfactory explanation of arrhythmia is obtainable may be one of tumor breaking through or originating in the main portion of the conducting system." Complete heart block has been reported with lymphangio-endothelioma,[3] hemangio-endothelioma,[4] myeloblastoma,[5] reticulum-cell sarcoma,[6] and leukemic infiltration of the interventricular septum.[7] Despite the frequent occurrence of myocardial involvement in leukemia, Dresdale and co-workers[7] could find only one other instance of complete atrioventricular block due to leukemic involvement when he reported his case in 1949.

Shelburne and Aronson[5] reported a case of complete atrioventricular block and pericardial effusion in a patient with a myeloblastoma of the cranium. When irradiation therapy was employed the effusion cleared and a normal cardiac rhythm returned.

It is the purpose of this paper to report a case of bronchogenic carcinoma, metastatic to the heart, with complete atrioventricular block as the only clinical manifestation of metastatic cardiac disease.

### Case Report

A 42-year-old white man was admitted to Cincinnati Veterans Administration Hospital on November 22, 1959. Six months prior to admission he developed retrosternal aching which did not radiate. A chest x-ray revealed a lesion in the right upper lobe. A physician noted that he had a slow heart rate (45 beats per minute) and an apical systolic murmur. There was no known history of heart disease. The patient observed palpitation during the month prior to admission but no edema, orthopnea, or paroxysmal nocturnal dyspnea. Mild shortness of breath and an intermittent cough with blood streaking were noted. He had smoked one pack of cigarettes per day for many years. There was no history of syncope. On admission his blood pressure was 130/70, and the ventricular rate was 45 beats per minute and regular. He was of normal weight and muscular development but appeared apprehensive. There was no cervical venous distention. In the right posterior area the chest was dull to percussion, the breath sounds were diminished, and no wheezes were audible. The point of maximum cardiac impulse was in the fifth left intercostal space in the midclavicular line. The apical first sound varied in intensity, and atrial sounds were heard in diastole. A grade II (of VI) systolic murmur was heard best over the left sternal border in the third intercostal space and it radiated to the cardiac apex. Abdominal examination was not remarkable. A firm movable subcutaneous nodule of 2½-cm. diameter was palpated at the left iliac crest. Another subcutaneous mass of 4-cm. diameter was palpated adjacent to the first and second lumbar vertebrae. There was moderate clubbing of the fingers and toes.

The hematocrit value was 42 per cent, and the white cell count was 8,300 per mm.$^3$ The serum glutamic oxaloacetic transaminase was 24 units. A posteroanterior roentgenogram of the chest showed an infiltrative lesion in the right upper lobe (fig. 1), interpreted as probable bronchogenic carcinoma. There was no cardiomegaly. X-rays of the lumbar spine demonstrated no abnormalities. An electrocardiogram showed complete atrioventricular block (fig. 2).

The patient was treated with sublingual isoproterenol (Isuprel), 10 mg. four times daily, and his ventricular rate varied between 32 to 56 beats per minute. A biopsy of the mass on the left iliac crest revealed poorly differentiated metastatic carcinoma.

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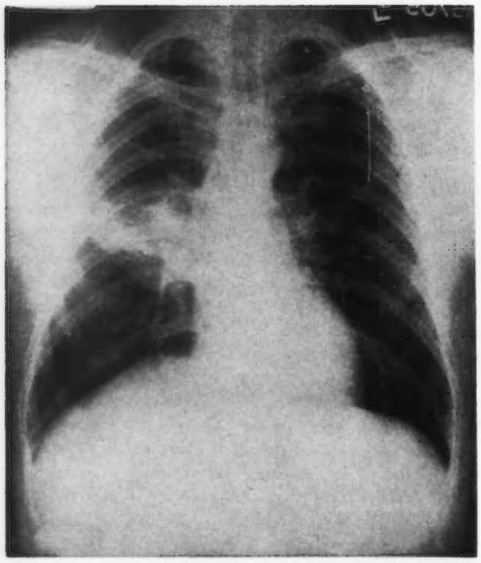

**Figure 1**

*Mass lesion within the right midlung field demonstrating a sharp undersurface. The cardiac silhouette is normal.*

The clinical diagnosis was bronchogenic carcinoma with metastases; cardiac infiltration by the tumor was thought to be probable. A course of nitrogen mustard and radiation therapy to the mediastinum was initiated. During the last week of hospitalization the patient developed substernal pain radiating down the left arm that required merperidine (Demerol) for relief. The electrocardiogram remained unchanged. On January 5, 1960, the patient developed mild generalized convulsions that became more severe, and he died 3 days later after one of these episodes. The cardiac rhythm did not change during this terminal episode.

The left lung weighed 600 Gm., and the right lung weighed 800 Gm. The right upper lobe bronchus was occluded by tumor at its origin. The bronchial lumen admitted only a 2-mm. probe. The tumor extended into the lung parenchyma, and several regional lymph nodes contained metastases. The tumor measured 4 by 5 cm. and contained extensive areas of necrosis and hemorrhage. The lung was congested beyond the tumor. The pulmonary vessels were not remarkable. The mediastinum contained several enlarged tumor-filled lymph nodes, most marked at the bifurcation of the trachea.

The heart weighed 450 Gm. and was thought not to be dilated. The pericardial cavity contained 30 ml. of clear serous fluid. The pericardium and epicardium were normal; the valves were normal but on the right side of the heart the interventricular septum appeared to be obliterated by a large tumor mass. The mass did not seem to bulge into the right cardiac chamber. The metastatic tumor measured 5 by 6 cm. (fig. 3). An additional 1½-cm. metastatic tumor nodule was found in the anterior wall of the left ventricle. The coronary arteries showed virtually no atheroma. No scarring or fibrosis of the myocardium was noted.

Additional metastases were found in both adrenal glands, the right kidney, the pancreas, and the left iliac spine. The brain was not examined.

Microscopic sections of the heart showed well-differentiated adenocarcinoma as did sections of the tumor of the lung (figs. 4 and 5).

## Discussion

At one time the prevailing opinion was that both primary and secondary tumors of the heart and pericardium were a rare occurrence. Cohen and associates,[8] however, analyzed 315 autopsies of malignant tumor cases; the incidence of cardiac involvement was 20.6 per cent. In a similar study by DeLoach and Haynes,[9] cardiac metastasis was observed in 13.8 per cent of 980 necropsies of patients who died with malignant disease. Scott and Garvin[10] discovered secondary cardiac involvement in 10.9 per cent of 1,082 cases of malignant disease that they reviewed. Hanfling,[11] in a similar survey, recently reported an incidence of 18.5 per cent in 694 cases.

Metastatic tumor of the heart has been said to be 20 to 40 times as common as primary tumor.[12] Four types of primary tumor are especially prone to cardiac metastases. These are carcinoma of the lung, carcinoma of the breast, malignant melanoma, and the group of hematopoietic malignancies (leukemia, lymphoma, myeloma). In one series (Scott et al.[10]) cardiac involvement was seen in 35.6 per cent of patients dying of bronchogenic or breast carcinomas. Bisel et al.[13] encountered cardiac infiltration in 52 of 119 patients with leukemia (44 per cent). Hanfling[11] found 46 per cent of 74 patients with leukemia had myocardial involvement.

The pathogenesis of cardiac metastasis involves one of three postulated mechanisms: 1. Direct extension from primary or secondary

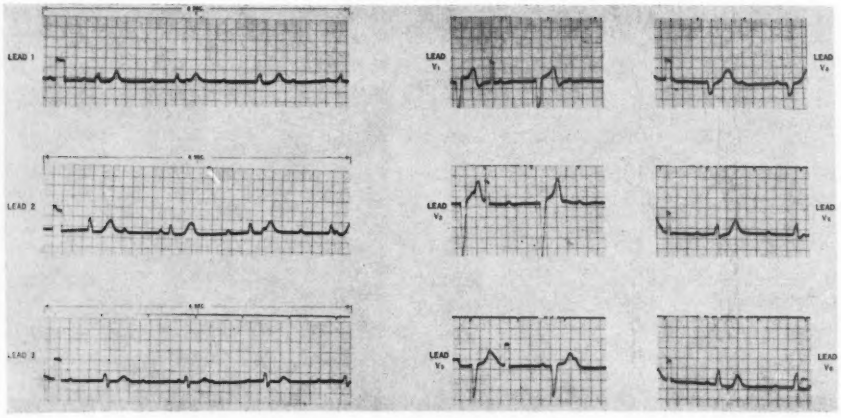

**Figure 2**

*Electrocardiogram showing complete atrioventricular block with idioventricular rhythm. The atrial rate is 82 per minute; the ventricular rate is 37 per minute.*

tumor of the lung or neighboring mediastinal structures. By this method the tumor may infiltrate the pericardium and subsequently invade the myocardium. 2. Tumor emboli may reach the heart via the coronary arteries as a result of intrathoracic neoplastic invasion of the pulmonary veins with subsequent spread to the left atrium, left ventricle, and aorta. This may give rise to miliary myocardial infarction due to tumor emboli. Multiple or single nodules may result from hematogenous dissemination. Blood stream spread from distal tumor sites other than thoracic structures is another postulated mechanism of cardiac metastasis. 3. Retrograde lymphatic extension from nearby intrathoracic structures may give rise to neoplastic lymphangitis.

The clinical aspects of metastatic tumor to the heart are varied. The triad of congestive heart failure, arrhythmias, and pericardial effusion leading to cardiac compression or tamponade are considered by Cohen et al.[8] suggestive of cardiac involvement of a previously normal heart in a patient with a malignant neoplasm. In Scott's study of 1,082 patients with malignant disease,[10] clinical evidence of heart disease was uncommon. When congestive heart failure was present the patient invariably had tumor invasion of the

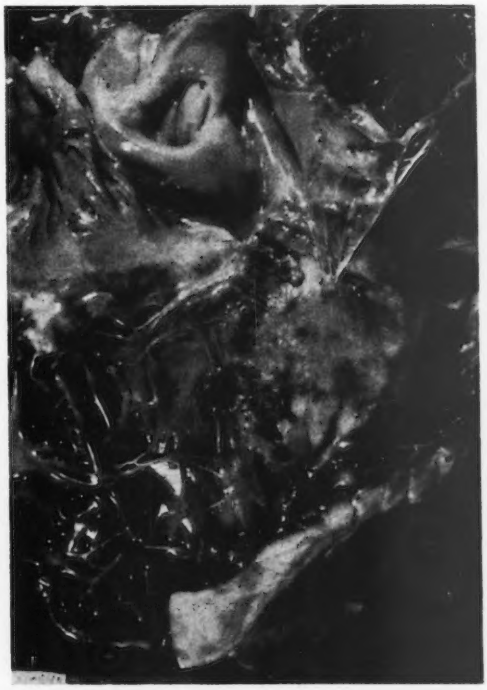

**Figure 3**

*Neoplastic nodule protruding into the right ventricle from the interventricular septum. The mass extends from the tricuspid chordae tendineae almost to the cardiac apex.*

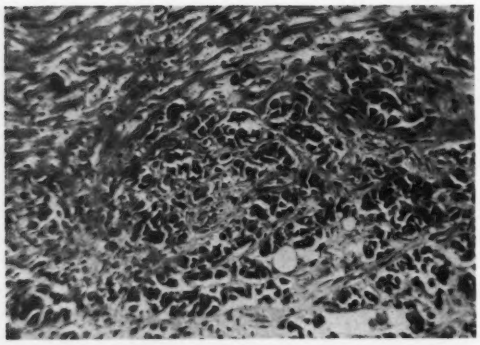

**Figure 4**

*Nests of anaplastic tumor cells are seen invading the myocardium. Hematoxylin and eosin stain.*

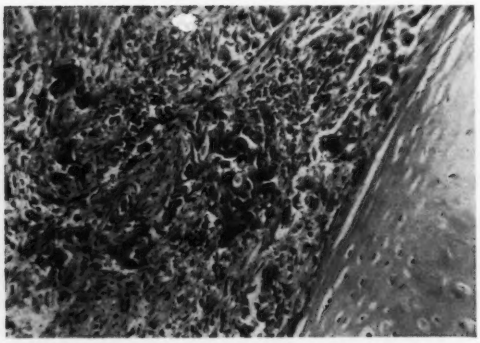

**Figure 5**

*Anaplastic tumor cells of bronchogenic carcinoma with dense stromal reaction are seen adjacent to cartilage in the bronchus of origin. Hematoxylin and eosin stain.*

heart. In 100 patients, selected so as to exclude those with metastatic cardiac disease, 7 had pericardial effusion and 2 had arrhythmias. Scott concluded that congestive heart failure is the most valuable sign, while arrhythmias and pericardial effusion are but suggestive signs of metastatic cardiac disease.

The most common arrhythmias associated with cardiac metastasis were atrial fibrillation, atrial flutter, and paroxysmal atrial tachycardia in separate studies by Auerbach et al.[14] and Cohen et al.[8] In most of these instances involvement of the right atrium was found.

Bisel et al.[13] found the electrocardiogram to be suggestive of cardiac involvement in 28.8 per cent of his cases. He found T-wave abnormalities to be the most consistent abnormality (14 per cent). He also reported S-T deviation and Q waves in some cases. In one interesting report by Fishberg[15] pain suggestive of myocardial infarction was the chief complaint of a patient with a cardiac tumor; at autopsy the tumor surrounded the left circumflex coronary artery.

Sudden death has been reported in patients with cardiac neoplasms, most frequently, however, in patients with primary cardiac tumor.[16] Cullpepper and Von Haam[17] reported a case of a patient with carcinoma of the liver who died suddenly and was found to have tumor thrombosis of the inferior vena cava protruding into the right atrium. They postulated sudden death resulting from ball-valve action of the tumor. Extensions of tumor masses to the heart via the great veins have been seen in hypernephroma, testicular neoplasm, lymphosarcoma, thyroid carcinoma, and bronchogenic carcinoma.[11, 16, 18, 19]

There have been case reports of cardiac rupture secondary to metastatic cardiac tumor,[20] as well as neoplastic involvement of the pericardium producing constrictive pericarditis.[21, 22]

## Summary

A partial review of the literature indicates that the heart is not infrequently involved in patients who have malignant disease. The most common tumors metastasizing to the heart are bronchogenic carcinoma, breast carcinoma, malignant melanoma, and the group of hematopoietic malignant tumors. The clinical triad of myocardial insufficiency, cardiac arrhythmia, and pericardial effusion involving a previously normal heart should alert one to this possibility, especially in a patient with known malignant tumor.

Complete atrioventricular block is a rather uncommon manifestation of metastatic cardiac tumor. A case is reported in which complete heart block appeared as the sole clinical manifestation of metastatic involvement of the heart by bronchogenic carcinoma. Necropsy revealed cardiac involvement by tumor

to be virtually limited to the interventricular septum.

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# Origin of the Right Pulmonary Artery from the Ascending Aorta

## Report of a Surgically Corrected Case

*By* Robert M. Armer, M.D., Harris B. Shumacker, M.D., and Eugene C. Klatte, M.D.

THE OCCURRENCE of a form of congenital heart disease in which there is an anomalous origin of the right pulmonary artery from the ascending aorta, with or without an associated patent ductus arteriosus, but no anomalous pulmonary venous drainage or intracardiac anomaly, is rare. Eight cases have been found on review. The purpose of this paper is to describe a surgically corrected case.

### Review of Literature

Findlay and Maier,[1] in 1951, reviewed the literature concerning anomalies of the pulmonary vessels and reported one case of their own that fits the category under discussion. She was a 4-month-old Negro girl with intermittent cyanosis, dyspnea, and fever. Her congestive heart failure improved initially with medical treatment but she soon died in severe failure and with extensive pneumonia. At autopsy there was a greatly enlarged heart but no intracardiac defect. Just distal to the aortic valve a large vessel originated from the left side of the aorta and coursed behind the esophagus to enter the right lung. There was no right pulmonary artery branch from the main pulmonary artery, and the ligamentum arteriosum was in the normal location. Right pneumonectomy and division of the anomalous pulmonary artery were proposed in retrospect as possible methods of treatment. Maier[2] discussed the same patient in 1954 and suggested that an essentially normal distribution of the blood flow to both lungs might have resulted from a surgical transfer of the proximal end of the anomalous artery from the aorta to the side of the main pulmonary artery.

Sikl[3] described the autopsy findings in a 4-month-old infant with this anomaly. There was an associated patent ductus arteriosus.

In May of 1960, DuShane et al.[4] reported such a malformation in a 2-month-old infant. This baby entered the hospital in severe congestive heart failure that did not improve with medical management. Venous cardiac catheterization demonstrated a bidirectional shunt via a patent ductus arteriosus. The right pulmonary artery could not be entered with the catheter. Angiocardiography was not performed. The infant did reasonably well for a few hours following division and suture of the patent ductus arteriosus but then deteriorated rapidly and died the day after the operation. The true situation was not appreciated until the postmortem examination. Edwards, in discussing embryologic considerations, thought that the origin of the right pulmonary artery from the ascending aorta possibly represented an abnormality in the evolution of the sixth right aortic arch, that is, persistence of its distal portion rather than its proximal part. Wagenvoort et al.[5] reported the autopsy study in another very young infant with this malformation.

Levine and Griffiths[6] are preparing a paper describing three cases discovered at autopsy. None had significant patency of the ductus arteriosus. These children were 3½ and 6½ months, and 2 3/4 years of age. One is the previously mentioned case of Findlay and Maier.

Vlad and Lambert[7] correctly diagnosed a case in an infant 4 months old by cardiac

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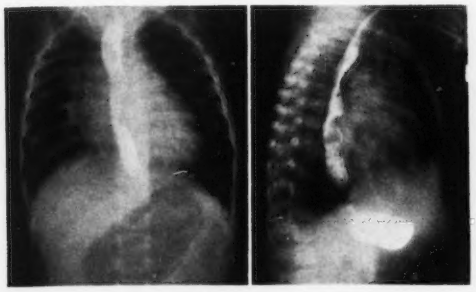

**Figure 1**

*Preoperative study January 4, 1960. There is enlargement of both ventricles and slight enlargement of the left atrium. The pulmonary vasculature is increased in both lungs but more so in the right than the left.*

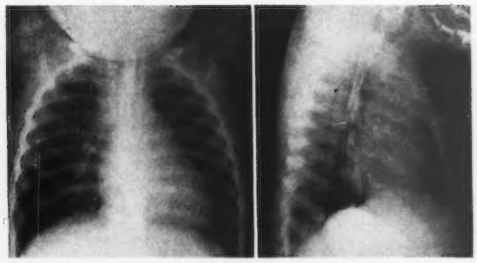

**Figure 2**

*Postoperative study June 1, 1960. The increased vasculature has returned to normal. The heart has decreased in size.*

catheterization and angiocardiography. The ductus was closed and the right pulmonary artery was ligated, following which there was dramatic relief of congestive heart failure but unfortunately the baby died 4 weeks later of pneumonia. Another infant of theirs died at 2½ months of age and was found at postmortem study to have this anomaly with a large patent ductus arteriosus.

## Case Report

### Clinical Findings

The patient was a 10-month-old white boy. The complaints were poor weight gain, repeated respiratory infections, and mild cyanosis associated with crying.

He was the first child of a 20-year-old mother. The course of the pregnancy and delivery were unknown, maternal serology was negative, and the infant's birth weight was 5 pounds 8 ounces. He was said to have breathed and cried spontaneously at birth. A heart murmur, systolic in time, maximal in the pulmonic area, and associated with a snapping pulmonic second sound was first detected at 3 weeks of age. At 6 weeks of age it was first noted that the infant was mildly cyanotic at times of stress. Repeated respiratory infections were treated with intramuscular antibiotics. At no time was the infant considered to be in obvious congestive heart failure, but his growth and development were retarded.

When hospitalized he was 10 months old and weighed 14 pounds 4 ounces. The respiratory rate was 36 per minute and not labored. The skin color was grayish but not obviously cyanotic. The thumbnails were slightly clubbed. He was small, poorly developed, poorly nourished, and unable to sit without support. The lungs were clear. The heart rate was 136 per minute and regular. There was a forward bulge of the precordium and a left parasternal right ventricular lift. The left border of cardiac dullness was midway between the midclavicular line and the anterior axillary line. Only an insignificant, vibratory type, grade I (on the basis of 5) systolic murmur was heard maximal at the lower left sternal border. There were no thrills. The pulmonic second sound was single, obviously accentuated, and snapping in character. The liver margin was sharp and palpable two fingerbreadths below the right costal margin in the right midclavicular line. There was no edema. The femoral pulses were normal. Blood pressure in the right arm was 90/45 mm. Hg and 105/? mm. Hg in the right leg.

Urine analysis was normal. The hemoglobin was 17.9 Gm. per cent, hematocrit value 50 per cent, and total white blood cell count 7,800 per $mm.^3$ with 26 per cent neutrophils and 74 per cent lymphocytes.

Radiographically (figs. 1 and 2) there was enlargement of both ventricles and the left atrium (fig. 1). A disproportionate increase of pulmonary vasculature in the right as compared with the left lung was not appreciated. There was incomplete right bundle-branch block and right ventricular hypertrophy on the electrocardiogram (fig. 3). The clinical impression was patent ductus arteriosus with moderate to severe pulmonary hypertension.

### Preoperative Physiologic Studies and Cineangiocardiography

Under general sedation a venous cardiac catheterization by the saphenous route was carried out at 12 months of age (table 1). The catheter passed easily through a patent ductus arteriosus into the descending aorta. The left pulmonary

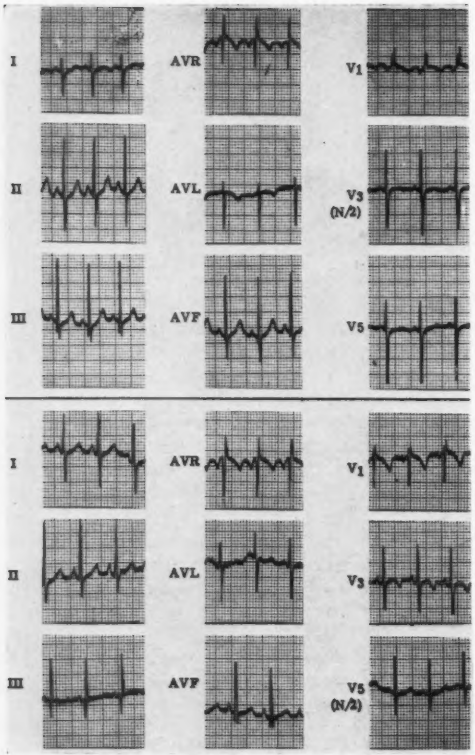


**Figure 3**

Top. *Preoperative electrocardiogram January 4, 1960. There is incomplete right bundle-branch block and right ventricular hypertrophy.* Bottom. *Postoperative study June 1, 1960. There has been a return toward normal with a change to a rSr' QRS configuration in $V_1$ and disappearance of the deep S wave in $V_5$.*

artery was entered repeatedly with the catheter, but the right pulmonary artery could not be located. This was not thought to be unusual at the time. The blood oxygen determinations were extremely erratic when the infant was breathing room air. Pressures in the pulmonary artery and the descending aorta were equal, 103/61 and 101/59 mm. Hg respectively. The sampling and pressures were then repeated with the patient breathing pure oxygen. Systemic pressure was unaltered, but there was a decrease in the pulmonary artery pressure creating a systolic gradient across the ductus arteriosus of 20 mm. Hg (fig. 4). A left-to-right shunt with an increase of 3.1 volumes per cent oxygen content from the right ventricle to the pulmonary artery was found.

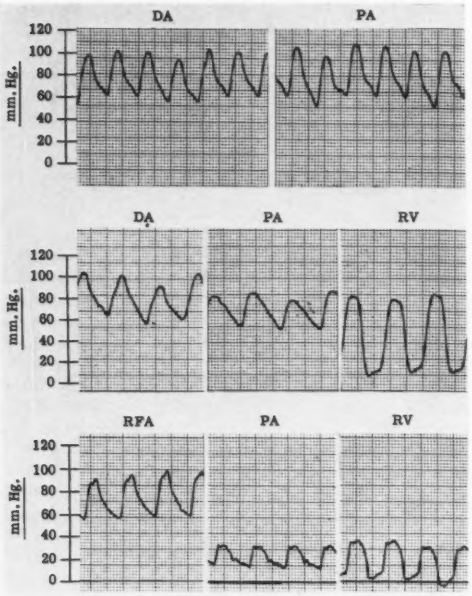


**Figure 4**

*DA, descending aorta; PA, pulmonary artery; RV, right ventricle; RFA, right femoral artery.* Top. *Pressure tracings February 16, 1960 prior to surgery. The descending aorta was entered via the patent ductus arteriosus. During breathing of room air the systemic and pulmonary artery pressures were equal.* Middle. *After breathing of pure oxygen. The systemic pressure is unaltered but the pulmonary artery pressure has decreased creating a peak systolic pressure gradient across the patent ductus arteriosus of 20 mm. Hg.* Bottom. *Three months after surgery.*

Fully saturated blood was obtained from the descending aorta, indicating no reversal of the flow while oxygen was being administered. The left atrium was entered through a patent foramen ovale but no shunt was found in either direction.

Selective cineangiocardiography was performed at the time of the cardiac catheterization. Serial filming at 30 frames per second was done during the injection of 90 per cent Hypaque-M* into the patent ductus arteriosus, the main pulmonary artery, the right ventricle, and the left atrium. The injection of contrast medium into the right ventricle opacified that chamber, the main pulmonary artery, the left pulmonary artery, the ductus ar-

*Hypaque brand of diatrizoic acid with methylglucamine concentrate: Winthrop Laboratories, New York 18, New York.

**Table 1**

*Cardiac Catheterization Data*

| | Preoperative study Age 12 months | | | Postoperative study Age 15½ months | |
|---|---|---|---|---|---|
| | Room air | | Pure oxygen | Room air | |
| | (Pressure, mm. Hg) | (Pressure, mm. Hg) | (Content of $O_2$ vol. %) | (Content of $O_2$ vol. %) | (Pressure mm. Hg) |
| IVC | — | 3.6 | 14.5 | 10.4 | 1.0 |
| SVC | — | 3.1 | 15.6 | 11.6 | 1.3 |
| RA | 5.4 | 1.0 | 14.1 | 11.9 | 0 |
| LA | 5.7 | 14.6 | 21.7 (100% saturation) | 16.5 (97% saturation) | 1.9 |
| RV | 101/5 | 82/9 | 15.5 | 11.5 | 32/5 |
| PA | 103/61 | 81/50 | 18.6 | 11.3 | 28/7 |
| DA | 101/59 | 101/59 | 22.2 (100% saturation) | — | — |
| RFA | 104/58 | — | — | 16.3 (97% saturation) | 100/60 |

Explanation of symbols: IVC, inferior vena cava; SVC, superior vena cava; RA, right atrium; LA, left atrium; RV, right ventricle; PA, pulmonary artery; DA, descending aorta; RFA, right femoral artery.

teriosus, and the descending aorta. The right pulmonary artery, however, did not fill (fig. 5). Following the injection into the left atrium a normal left atrium and ventricle with intact septa were noted. There was simultaneous opacification of the ascending aorta and the right pulmonary artery and its branches.

To clarify better the origin of the blood flow to the right lung a retrograde arterial cineangiocardiogram by way of the right brachial artery was carried out. The catheter tip was positioned just distal to the aortic valve for the injection of contrast medium. It was conclusively demonstrated that the right pulmonary artery arose as a single vessel from the posterior aspect of the ascending aorta (fig. 6).

Once the diagnosis was known examination showed minimal but definite signs of early clubbing and faint cyanosis of the nailbeds, more pronounced in the left arm than in the right.

**Operative Procedure**

At surgery a T-shaped sternal incision was made. The ascending aorta was enlarged and appeared dilated beyond the aortic valve. A large right pulmonary artery arose from the posterior surface of the aorta. Its diameter was judged to be 12 or 13 mm., approximately the size of the aorta at that level. Just distal to the origin of the left subclavian artery the aorta narrowed somewhat to a diameter of 6 or 7 mm. The ductus arteriosus extended from the end of the pulmonary trunk to the narrowed portion of the distal aortic arch. It was approximately the same size as the aorta at that location. The pulmonary trunk then continued as the left pulmonary artery (fig. 7). Systolic pressures in each of these structures were essentially equal. After dissection of the various vessels the right pulmonary artery was clamped and its point of origin from the aorta was closed with sutures. The ductus arteriosus was divided between clamps and both ends were sutured. Finally, the anterior portion of the main pulmonary trunk was clamped with a curved vascular clamp in such a way as to permit a longitudinal incision, and a stretch-weave Dacron graft with a diameter of 13 mm. was interpolated anterior to the aorta end-to-side between the distal end of the right pulmonary artery and the pulmonary trunk. The surgery was well tolerated.

**Postoperative Course**

The postoperative course was uncomplicated. Although the child had not been in respiratory distress prior to surgery, it was soon evident that he breathed a great deal easier after surgery. He was discharged on the fourteenth day after the operation.

Six weeks following surgery, at the age of 14 months, the patient weighed 18 pounds 14 ounces, a postoperative gain of 3 pounds 14 ounces. He had improved in all respects. The heart was slightly enlarged to the left by percussion but not overactive. There was a faint systolic murmur in the pulmonic area. The pulmonary second sound was single and regarded as being at the upper limits of normal in intensity.

The cardiac status was re-evaluated 3 months after surgery when the infant was 15 months old. On the postoperative radiographs the con-

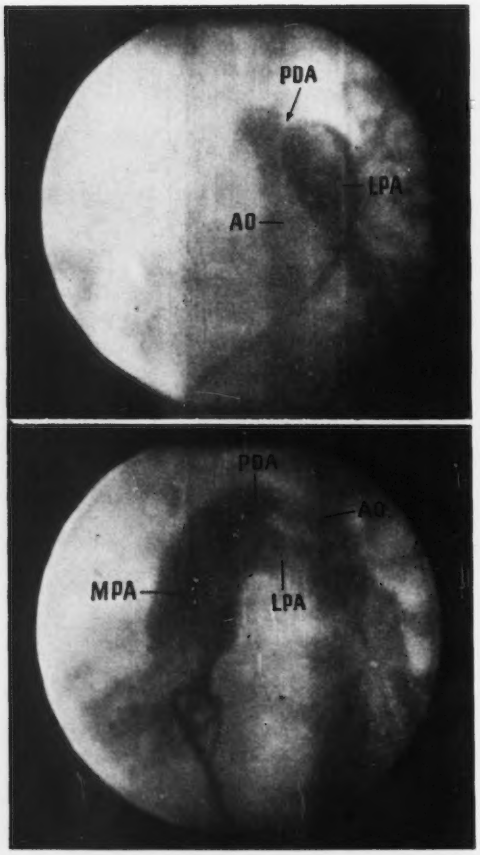


**Figure 5**

*Preoperative selective cineangiocardiogram.* Top. *Posteroanterior projection. Injection site: main pulmonary artery. Note main pulmonary artery, left pulmonary artery, patent ductus arteriosus, and aorta. The right pulmonary artery is not visualized.* Bottom. *Left anterior oblique projection. Injection site: right ventricle. Note main pulmonary artery, left pulmonary artery, patent ductus arteriosus, and aorta.*

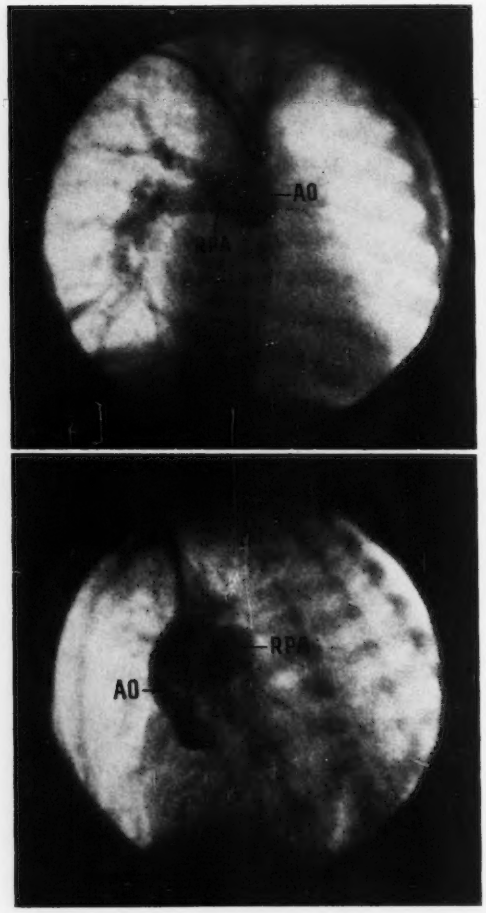


**Figure 6**

*Preoperative selective cineangiocardiogram.* Top. *Posteroanterior projection. Injection site: ascending aorta. Note aorta and right pulmonary artery.* Bottom. *Left anterior oblique projection. Injection site: ascending aorta.*

gestive changes in the lungs had cleared. No unusual chamber enlargement was noted but there was a prominent bulge along the right superior paramediastinal area (fig. 2). The electrocardiogram had returned toward normal (fig. 3). The findings at right heart catheterization were regarded as within normal limits except for mild elevation of the right ventricular pressure (32/5 mm. Hg). The pulmonary artery pressure was 28/7 mm. Hg (fig. 4). Again there was no evidence of an intracardiac shunt (table 1). Cineangiocardiography proved the surgical anastomosis to be widely patent (fig. 8).

## Discussion

Although anomalous origin of the right pulmonary artery from the ascending aorta with or without a patent ductus arteriosus is uncommonly encountered, its recognition is essential for proper patient management, since

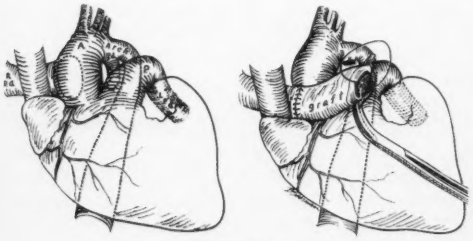

**Figure 7**

Left. *Anomalous origin of the right pulmonary artery from the posterior aspect of the ascending aorta with an associated patent ductus arteriosus.* Right. *Method of surgical correction.*

it is a surgically correctable condition. Symptoms tend to appear early and to be severe. There are two features that might aid one in suspecting the diagnosis. If radiographic study shows a disproportionate or unilateral increase in pulmonary vasculature, this condition should be considered. If a patent ductus arteriosus were present, a difference in color and clubbing in the arms might be evident. Angiocardiography is of prime importance and the only certain method of delineating the anomaly.

While the prognosis in the case presented must remain uncertain pending long-term observation, there is reason to believe the outcome will be good. The excellent response of the pulmonary vascular bed in a 1-year-old child, in whom the pressure previously was equal to systemic, is very encouraging. Fortunately it was possible to utilize a graft of such size that it should permit good perfusion of the right lung despite growth.

As far as we can ascertain this is the first case in which a graft has been used successfully in the pulmonary arterial tree. The problem has, however, been subjected to experimental study. Robinson, Glotzer, Gilbert, and Hurwitt[8] showed that aortic homografts in the pulmonary artery are subject to severe degenerative alterations. Moore and his associates[9] in our laboratory demonstrated that plastic tubular grafts work well when interposed in the pulmonary arteries. After surgery in our patient, Sarrvage, Rudolf, and Gross[10] reported on the experimental utilization of pericardial grafts for pulmonary artery replacement.

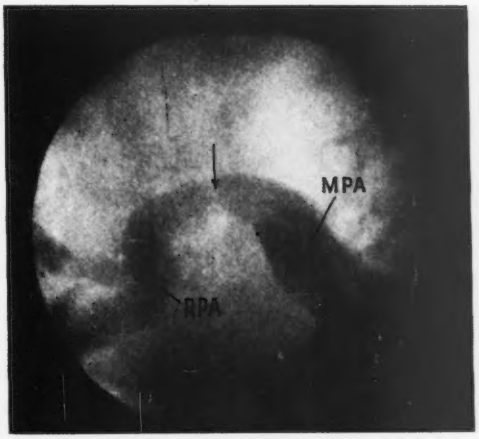


**Figure 8**

*Postoperative selective cineangiocardiogram. Posteroanteror projection. Injection site: main pulmonary artery. Note wide patency of the tubular plastic graft interposed between the right and main pulmonary arteries (arrow).*

A survey of the literature has revealed no other case of successful complete surgical correction of this defect.

## Summary

A case of anomalous origin of the right pulmonary artery from the ascending aorta with an associated patent ductus arteriosus has been described. Successful complete surgical correction was accomplished after physiologic and cineangiocardiographic studies had established the diagnosis. Postoperative evaluation demonstrated a return to nearly normal physiologic values. The unparalleled value of selective angiocardiography in the anatomic assessment of cardiovascular lesions is emphasized.

## Addendum

Additional reference: Caro et al.* reported a 23-year-old man with aortic origin of the right pulmonary artery and patent ductus arteriosus. The anomalous pulmonary vessel was stenotic at its origin, which

*Caro, C., Lermanda, V. C., and Lyons, H. A.: Aortic origin of the right pulmonary artery. Brit. Heart J. 19: 345, 1957.

may have accounted for the absence of symptoms until the age of 17 years. Diagnosis was established by cardiac catheterization and angiocardiography. Surgical correction by an Ivalon graft with end-to-end anastomosis to the right pulmonary artery and end-to-side anastomosis to the main pulmonary artery was accomplished; however, the patient died 5 hours after completion of surgery.

Our patient has been examined 15 months after surgery. He has grown and developed normally and is asymptomatic. A soft systolic murmur persists at the base of the heart, but examination otherwise is normal.

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Errors in judgment must occur in the practice of an art which consists largely in balancing probabilities.—SIR WILLIAM OSLER. *Aphorisms from His Bedside Teachings and Writings.* Edited by William Bennett Bean, M.D. New York, Henry Schuman, Inc., 1950, p. 124.

# Isolated Anomalous Connection of a Great Vein to the Left Atrium

## The Syndrome of Cyanosis and Clubbing, "Normal" Heart, and Left Ventricular Hypertrophy on Electrocardiogram

*By* W. R. Meadows, M.D., Ingemar Bergstrand, M.D., and J. T. Sharp, M.D.

THE FINDINGS of cyanosis and clubbing not explained by diffuse pulmonary disease and in the presence of a normal heart on physical examination suggest pulmonary arteriovenous fistula. Absence of electrocardiographic evidence of right ventricular hypertrophy and a normal right ventricular pressure on catheterization are further evidence for this diagnosis. The present case, the fourth of its kind to appear in the literature, shows that when the electrocardiogram under these conditions exhibits left ventricular hypertrophy without evident cause, the most probable diagnosis is isolated anomalous connection of a great vein to the left atrium.

### Case Report

A 37-year-old Negro was referred to the cardiopulmonary laboratory for evaluation of cyanosis, clubbing, and polycythemia. He had been hospitalized since May 1954 for active pulmonary tuberculosis.

Except for frequent headaches, especially as a child, there were no symptoms attributable to the findings. There was no history of dyspnea, exercise intolerance, or other symptoms of cardiac insufficiency. Clubbing of the fingers had been present for as long as he could remember but had not attracted any attention prior to the present hospitalization. He worked at heavy manual labor, and during the war he had no trouble keeping up with the other men during periods of rigorous training.

The patient's father, one of his five brothers, and two of his six sisters were said to have died of heart trouble, the father while the patient was still a child, the brother at age 38, and the sisters at ages 40 and 46. Another sister is living with a heart condition at age 42. His one child is in good health.

The report of the autopsy on his brother revealed a patent foramen ovale 14 mm. in diameter, marked dilatation, hypertrophy, and fibrosis of the right ventricle, and moderate pulmonary arteriosclerosis. A small anteroseptal myocardial infarction was present although there was no coronary sclerosis. Other findings included pulmonary tuberculosis of the right upper lobe and clubbing of the fingers and toes.

The patient was well developed and showed no wasting from his tuberculous disease. Marked clubbing of the fingers and cyanosis and suffusion of the conjunctivae, buccal mucosa, and tongue were present. No murmurs were heard. The first heart sound was normal, but the second was not split. A transient early diastolic "filling sound" was audible at the apex immediately after lying down and upon raising the legs. Except for post-tussic rales in the left apex the remainder of the examination was unremarkable. The blood pressure was 110/75.

Chest x-rays including lateral and both oblique views revealed bilateral far advanced cavitary tuberculosis, but the heart size and configuration were normal. Barium studies showed no evidence of an abdominal situs inversus. Electrocardiograms for years had consistently shown the T-wave changes commonly ascribed to left ventricular hypertrophy, a P-R interval of 0.24 to 0.26 second, notching of P waves in leads II, III, and $aV_F$, and occasional wandering of the pacemaker to the atrioventricular node (fig. 1).

The hemoglobin had varied from 15 to 21.7 Gm., and the hematocrit value had been as high as 74 per cent. In January 1955 the blood volume was found to be 35 per cent above the predicted value; the cell volume was increased by 56 per cent while the plasma volume was normal. The arterial oxygen saturation at this time was 82 per cent, and the oxygen capacity was 25.97 volumes per cent; the arterial $pCO_2$ was 42 mm. Hg. The arterial oxygen saturation was again

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Supported in part by grants H-3170 and HTS-5447, National Heart Institute, U. S. Public Health Service.

**Table 1**

*Catheterization Data*

| Catheter site | Right heart catheterization via SVC 9/20/60 | | | Left heart catheterization via IVC 10/28/60 | | |
|---|---|---|---|---|---|---|
| | % Oxygen saturation | Pressure in mm. Hg S/D | Mean | % Oxygen saturation | Pressure in mm. Hg S/D | Mean |
| Right atrium | 63 | | | | | |
| Right ventricle | 61 | 23/3 | | | | |
| Pulmonary artery | 67 | 18/8 | | | | |
| Left pulmonary vein | | | | 100+ | | |
| Right pulmonary vein | | | | 100+ | | |
| Left atrium | | | | 100+ | | 3 |
| Inferior vena cava | | | | 74–79 | | |
| Radial artery | 79 | 106/67 | 80 | 85–88 | 116/68 | 83 |
| $O_2$ consumption* | 275 ml./min. | | | 275 ml./min. | | |
| Blood $O_2$ capacity† | 26.1 vol. % | | | 26.1 vol. % | | |
| Systemic A-V diff. | 3.9 vol. % | | | 3.3 vol. % | | |
| Pulmonary A-V diff. | 8.6 vol. % | | | 6.8 vol. % | | |
| Ratio of systemic to pulmonary flow | 2.2 | | | 2.1 | | |
| Systemic flow | 4.2 L./min./M.$^2$ | | | 5.1 L./min/M.$^2$ | | |
| Pulmonary flow | 1.9 L./min./M.$^2$ | | | 2.5 L./min./M.$^2$ | | |
| Systemic vascular resistance | 914 dynes sec. cm.$^{-5}$ | | | 790 dynes sec. cm.$^{-5}$ | | |
| Pulmonary vascular resistance | 250 dynes sec. cm.$^{-5}$ | | | | | |

BSA = 1.65

*Oxygen consumption was determined on 11/8/60.

†Blood $O_2$ capacity was calculated from the hemoglobin determination of 19.5 Gm. per cent on 9/14/60; six hemoglobin determinations within the previous year had varied from 18.2 to 20.3 Gm. per cent.

The anatomic situation prevented the obtaining of a true mixed venous blood sample for determination of oxygen content and calculation of systemic flow. In lieu of this a pulmonary artery sample was used for the calculation of systemic flow during the first catheterization while a high inferior vena caval sample was used for the calculation of both systemic and pulmonary flows during the second catheterization. Analysis of data on 30 cases without shunts in this laboratory showed no significant difference in the oxygen content between samples taken from the superior vena cava and samples from the pulmonary artery. From this it is inferred that the oxygen content of inferior vena caval blood is not enough different from that of the superior vena caval blood to alter the oxygen content of the mixed venous blood. Otherwise stated, the oxygen contents of superior and inferior vena caval blood are essentially the same.

found to be 82 per cent in April 1960 and rose only to 92 per cent on breathing 100 per cent oxygen for 10 minutes. This submaximal rise in oxygen saturation was considered to be indicative of a sizable anatomic right-to-left shunt.

Pulmonary function studies revealed a vital capacity of 3.85 liters, a minimally depressed one-second timed vital capacity of 77 per cent, and a maximal breathing capacity of 107 L./min. (81 per cent of normal). The nitrogen washout curve was normal, and the alveolar nitrogen after 7 minutes of breathing 100 per cent oxygen was 1.7 per cent, these findings indicating a normal distribution of inspired air in the lungs. The residual volume was 0.88 liters or 70 per cent of normal and made up 19 per cent of the total lung capacity of 4.73 liters. The single-breath carbon monoxide pulmonary diffusing capacity of 8.8 ml. CO/min./mm. Hg/M.$^2$ of body surface area was slightly below normal and was thought

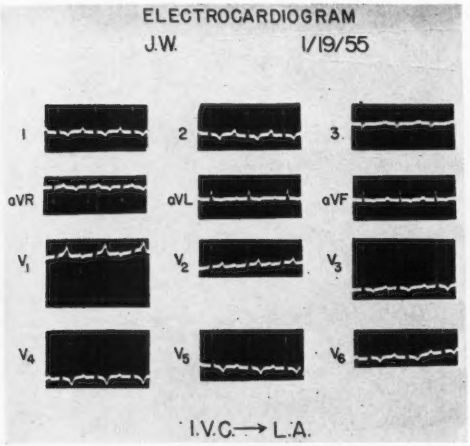


**Figure 1**

*Electrocardiogram showing changes consistent with left ventricular hypertrophy.*

to be compatible with the low pulmonary blood flow found on catheterization and the extent of his pulmonary tuberculosis. It was not considered sufficiently low to produce the degree of arterial oxygen unsaturation that was present.

Right heart catheterization was performed on September 20, 1960, via a branch of the left basilic vein and again on October 28, 1960, from the right saphenous approach (table 1). On the first occasion the catheter approached the right atrium in the usual manner, but some difficulty was experienced at this point before it entered the right ventricle. It then passed superiorly and somewhat to the right of the expected course of the right ventricular outflow tract to enter the pulmonary artery. Blood oxygen saturations in the right atrium, right ventricle, and pulmonary artery were 63.4, 61.0, and 67.1 per cent, respectively, whereas pressures measured in the latter two chambers were 23/3 and 18/8. A pulmonary angiogram visualized a normal vascular tree on the left, but technical difficulties prevented visualization of the right pulmonary arteries. From the saphenous vein the catheter passed superiorly into the cardiac shadow and then almost immediately into a left pulmonary vein from which fully saturated blood was withdrawn. A careful pull back with spot films and repeated blood sampling indicated that the catheter tip passed into a chamber within the heart shadow containing fully oxygenated blood. This was presumed to be the left atrium. It was then withdrawn into the inferior vena cava from which blood with saturations from 74 to 79 per cent was obtained.

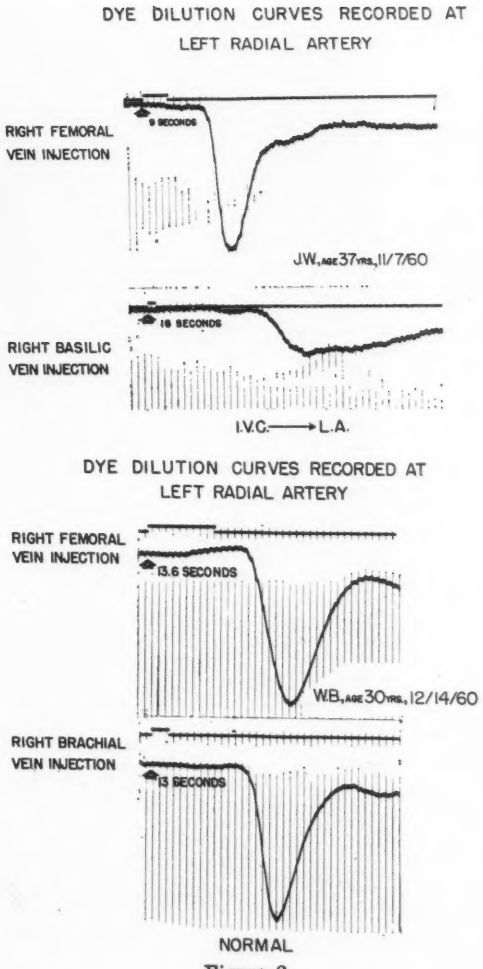


**Figure 2**

*Dye-dilution curves recorded from the left radial artery on patient J. W. (A, top) and on a normal subject (B, bottom) following femoral and brachial vein injection. The slight deviation from the baseline at 11 seconds in the basilic vein injection of J. W. is within the limits of baseline instability and was not observed on another curve following injection from the same site.*

During an unsuccessful attempt to catheterize the left ventricle the catheter passed into the right inferior pulmonary vein. Blood in this vein was fully saturated, a finding that excludes an arteriovenous fistula in the parenchyma drained by that vein.

Dye-Dilution Studies: Indocyanine green in-

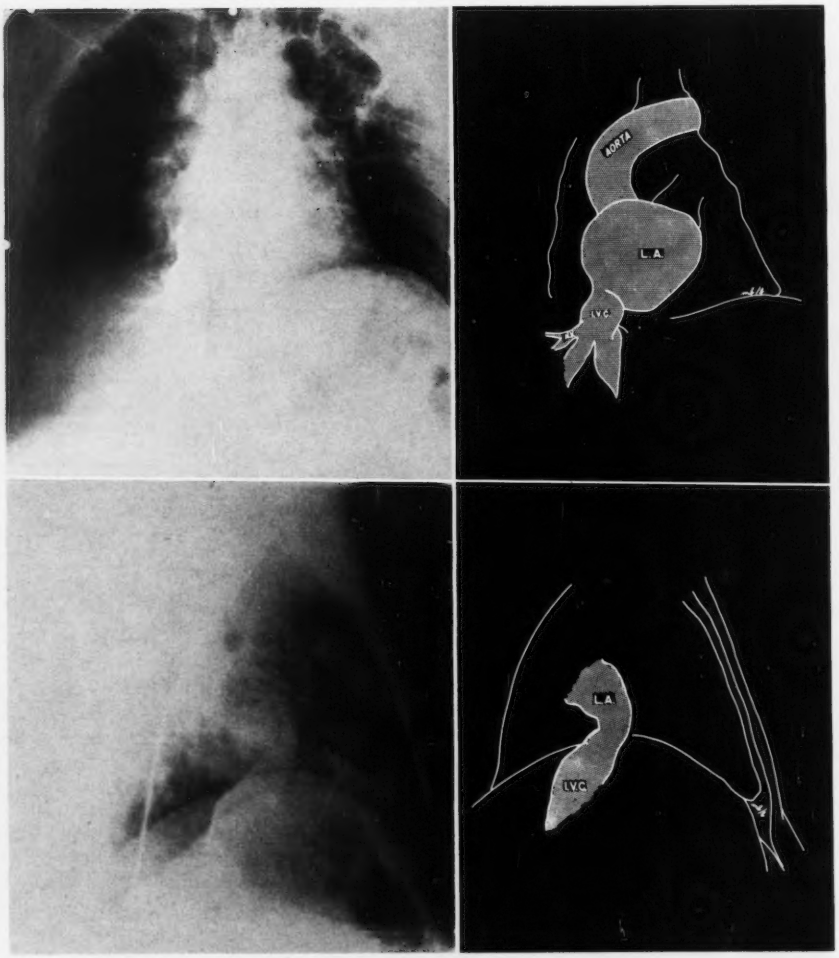


**Figure 3A**

*Anteroposterior and lateral angiocardiograms from inferior vena caval injection and their schematic interpretations. Left atrial, left ventricular, and aortic filling (left ventricle not clearly outlined here was well visualized on other frames). No right ventricular or pulmonary artery filling occurred.*

jected into the pulmonary artery appeared at the right radial artery in 9 seconds (first trial) and 12 seconds (second trial). On November 7, 1960, injections of dye were made alternately from the right femoral and right cubital veins and were recorded from the left radial artery. The average appearance time from the femoral vein (three recordings) was 9 seconds and that from the cubital vein (two recordings) was 17 seconds. The curves were in addition markedly dissimilar in contour (fig. 2).

Venous angiocardiograms were done at Billings Memorial Hospital on November 30, 1960. Injections of Hypaque from the inferior vena cava showed only the left heart chambers and aorta, whereas a similar injection from the right cephalic vein outlined the superior vena cava, right heart chambers, and pulmonary artery exclusively (fig. 3). The main pulmonary artery was again noted to be displaced medially but was anterior to the aorta.

Because of the additional risk in the presence

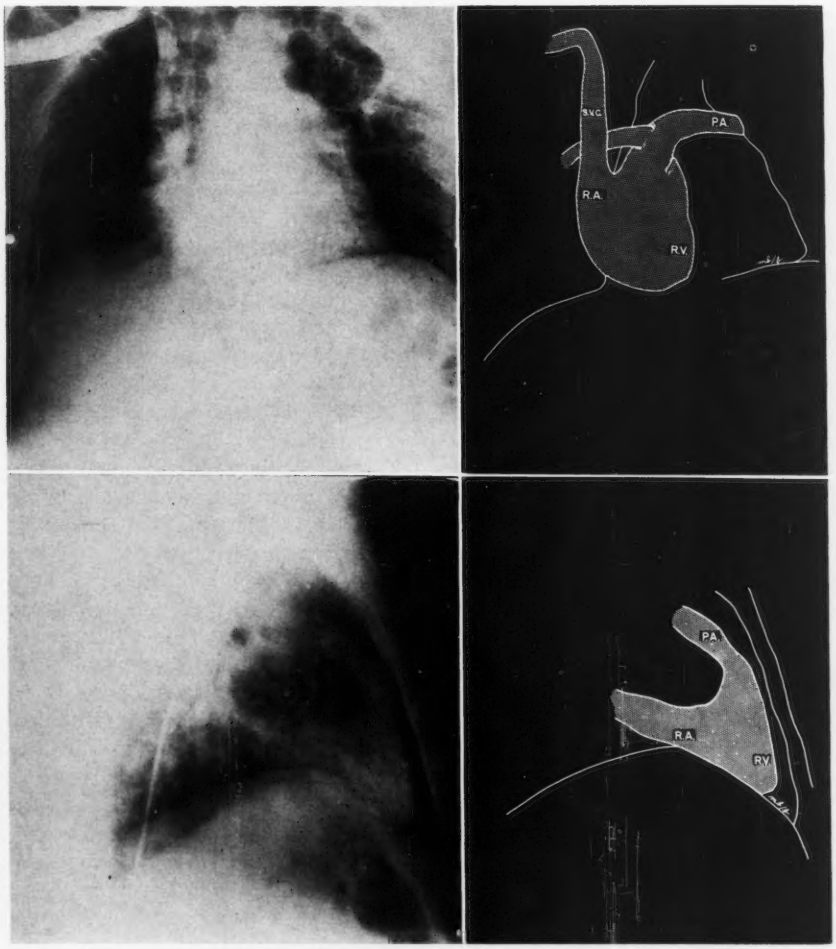


**Figure 3B**

*Anteroposterior and lateral angiocardiograms from right cephalic vein injection. The right ventricle and pulmonary artery are visualized.*

of far-advanced pulmonary tuberculosis and the lack of evidence that the tuberculous disease would be improved by normalizing his pulmonary flow or correcting his cyanosis, a decision for surgical intervention has not been made.

## Discussion

The recent literature contains descriptions of two cases of a solitary superior vena cava[1, 2] and one of an inferior vena cava[3] in which isolated anomalous drainage into the left atrium was present. It is remarkable that Taussig's text,[4] the reviews of Abbott[5] and Monckeberg,[6] and to our knowledge all other pertinent medical literature prior to 1955 do not mention these isolated anomalies although instances complicated by associated intracardiac defects are to be found.[7] The latter are usually serious, frequently associated with levocardia, and only rarely compatible with survival to adulthood.

Each of the three previously reported cases was cyanotic, and all had some degree of ef-

**Table 2**

*Systemic Venous Return*

| | Present case | | Tuchman's case |
|---|---|---|---|
| | 9/20/60 | 10/28/60 | |
| SVC | 2.5 L./min. or 36% | 3.5 L./min. or 38% | 3.2 L./min. or 38% |
| IVC | 3.8 L./min. or 54% | 4.8 L./min. or 52% | 4.4 L./min. or 52% |
| CS | 0.7 L./min. or 10% | 0.9 L./min. or 10% | 0.9 L./min. or 10% |

fort intolerance, which is in contrast to the case reported here. The electrocardiograms of two[2, 3] showed the T-wave changes of left ventricular hypertrophy while the tracing of the 10-year-old girl with isolated drainage of the superior vena cava into the left atrium was normal except for an S in $V_2$ of 28 mm.[1] Her diagnosis was proved by angiocardiography, and she was living with only slight disability, not warranting surgical correction, at the time of the report. The 15-year-old boy with the same anomaly died following surgical interference,[2] and the 32-year-old woman with anomalous drainage of the inferior vena cava collapsed and died suddenly while leading a comparatively active life.[3]

Two reports of bilateral superior venae cavae in which the left cava drained into the left atrium as an isolated anomaly are also to be found.[8, 9] In the one with a left-to-right shunt via the left innominate vein the left superior vena cava opened into the left atrium together with the left superior pulmonary vein.[8] The other with a similar anatomic situation had minimal electrocardiographic evidence of left ventricular hypertrophy and cyanosis, which disappeared following ligation of the aberrant vessel.[9] Both had a communication between the right and left superior venae cavae, and there was no readily apparent reason for the difference in shunting. We would like to suggest, however, that a difference in left ventricular distensibility due to the previously corrected aortic coarctation of the first case may have been the determining factor.

Although there were no clinical data to suggest an atrial septal defect, and the first catheterization by way of the superior vena cava had shown no arterialization of the right heart, the possibility of such a defect had to be considered when the catheter passed from the inferior vena cava into the pulmonary veins. In addition the dye-dilution curve from the cubital vein was compatible with a left-to-right shunt (fig. 2A, bottom curve), and although a controversial point, certain authorities believe that rare instances of atrial septal defect uncomplicated by pulmonary hypertension may be cyanotic from infancy.[1, 10] Since radiopaque dye injected into the right cephalic vein sharply delineated the right heart chambers and pulmonary artery and when injected into the inferior vena cava outlined only the left heart chambers and aorta, we believe that such absolute separation of blood returning from the two venae cavae most probably indicates anatomic partition. Complete selective streaming of inferior vena caval blood through an atrial septal defect without any right atrial mixing with blood returning from the superior vena cava would be virtually impossible.

The salient feature of the dye-dilution curves (fig. 2) is the abnormally short appearance time following femoral vein injection. This feature plus the single primary peak characterizing this curve can only be explained by a direct communication between the inferior vena cava and the left heart. Examination of dye curves recorded following brachial and femoral injection in two normal subjects (fig. 2B) and one patient with an atrial septal defect and a right-to-left shunt revealed a maximum difference of one second between brachial injection and femoral injection appearance times. In our patient brachial injection appearance time was 7 seconds more than femoral appearance time.

Two features less striking but also requiring explanation are the abnormal shape of the curve recorded following brachial vein injection and the absence of clearly defined recir-

culation deflections in either curve. We believe that both these abnormalities are explained by the occurrence of equal but small recirculations (first inferior caval, then superior caval via the pulmonary veins) at 8- or 9-second intervals rather than the larger, more widely spaced (13 to 16 seconds) recirculations that are present normally. An injected bolus of dye would be clearly definable as a distinct concentration peak only the first time around as in the upper curve of figure 2A.

Although flows cannot be estimated with precision, there is at least reasonable agreement between the outputs as calculated from the two catheterizations especially with respect to the systemic-to-pulmonary ratio (table 1). Since systemic flow is equal to the total venous return while pulmonary flow is limited to the return via the superior vena cava and coronary sinus, it becomes possible to estimate the separate caval flows. With coronary flow assumed to be 10 per cent of the total,[11] these values were calculated for our patient and the one reported by Tuckman et al.[2] (table 2). It will be noted that there is close agreement between the per cent values obtained.

Since the inferior vena caval flow and presumably all the pulmonary venous return enter the left atrium, pulmonary inflow and consequently pulmonary venous outflow is less than it would be normally. These considerations lead one to predict that in the absence of attempts at compensation systemic blood flow would be normal and pulmonary blood flow one-third[12] to one-half normal. In the presence of low pulmonary blood flow a normal oxygen uptake is maintained by two mechanisms that increase the oxygen-carrying capacity of the blood flowing to the lungs. One of these, polycythemia, is seen in the presence of arterial hypoxemia and provides for a widening of the arteriovenous oxygen difference in terms of volumes per cent without necessarily an associated widening in terms of oxygen saturation or $pO_2$. Thus, despite arterial hypoxemia, a normal mixed venous oxygen saturation ($pO_2$) may often be maintained, indicating adequate tissue-oxygen delivery. The other mechanism, seen in the absence of arterial hypoxemia, necessarily involves a widening of the arteriovenous difference by lowering the mixed venous oxygen saturation (tension) and is accompanied by inadequate tissue-oxygen delivery.

Our patient's moderate polycythemia was obviously one adaptation enabling him to take up oxygen normally and at the same time to maintain a normal mixed venous oxygen saturation. A moderate increase in left ventricular output appeared to be a further compensation. This provided an increase in total venous return including, importantly, superior vena caval return and hence augmented pulmonary blood flow. The mechanisms involved are not known. In the nearly analogous situation of pulmonary arteriovenous fistula, the systemic output is not usually increased nor has the left ventricle usually been hypertrophied as in this and analogous anomalies. A brief review of recent literature on pulmonary arteriovenous fistula further revealed no relationship between the level of arterial hypoxemia and the systemic output. Hypoxemia alone then would not explain the high systemic output.

One may consider partial anomalous systemic venous drainage into the left atrium to be analogous, but in reverse, to partial anomalous pulmonary venous drainage into the right atrium. In the former, pulmonary flow is low and systemic flow high; in the latter, the reverse is true, pulmonary flow exceeding systemic flow. Though facilitating understanding of some features of the former syndrome, realization of this analogy is not helpful in explaining the high systemic flow in anomalous systemic venous drainage into the left atrium. Indeed it brings up the question why in anomalous pulmonary venous drainage the pulmonary flow is not normal and systemic flow low, rather than the well-known pattern of slightly depressed to normal systemic flow accompanied by high pulmonary flow. Anatomic considerations explain adequately why pulmonic and systemic flows are in a given ratio to one another but leave unclear what the absolute flow values will be.

This aspect of the regulation of cardiac output in human disease warrants more investigation.


### Summary

A case is reported of isolated anomalous drainage of the inferior vena cava into the left atrium, the second in the literature and the first with catheterization data and dye-dilution curves. The anomaly is reflected by a well-defined clinical syndrome, is compatible with full cardiac competence at least until middle life, and should be relatively simple to correct surgically.



### Acknowledgment

We wish to express our appreciation to Drs. Benjamin M. Gasul and Harry A. Bliss for their suggestions during the preparation of the manuscript, to Dr. Meilute Indreika, for her assistance in reviewing the pertinent older foreign literature, to Dr. Lester Cohn, for his cooperation in the study of the patient, and to Miss Marian B. Berman and other members of the Medical Illustration Service, Hines V.A. Hospital, for their assistance in preparing the illustrations.


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## Art and Science

In art and letters, personality dominates everything. There we are concerned with a spontaneous creation of the mind, that has nothing in common with the noting of natural phenomena, in which the mind must create nothing. The past keeps all its worth in the creations of art and letters; each individuality remains changeless in time and cannot be mistaken for another. A contemporary poet has characterized this sense of the personality of art and of the impersonality of science in these words—"Art is myself; science is ourselves."—Claude Bernard. *An Introduction to the Study of Experimental Medicine.* New York, The MacMillan Company, 1927, p. 42.

# CLINICAL PROGRESS

## The Clinical Significance of the Pulmonary Collateral Circulation

*By* ALFRED P. FISHMAN, M.D.

THE NORMAL LUNG contains two distinct circulations of strikingly different origins, proportions, and functions. On the one hand is the huge pulmonary circulation, which originates in the right heart and pours the entire venous cardiac output into the lungs for gas exchange; on the other, is the diminutive systemic circulation, which delivers oxygenated blood to the lungs for the sustenance of its tissues, nerves, vessels, and conducting airways. Vascular connections between the two circulations are sparse and require elaborate injection technics for their display. Among the most elusive of these communications are the precapillary vessels that join pulmonary to bronchial arteries (fig. 1).

The systemic blood supply of the lung undergoes a remarkable proliferation in various disorders of the heart and lungs:[1-4] old vessels enlarge and become tortuous; new vessels appear and join with the old to form bizarre medusan patterns. And, in contrast to the normal lung, in which precapillary communications between the two circulations are difficult to demonstrate, the enlarged precapillary anastomoses between the pulmonary and systemic circulations are readily apparent.

There are several popular synonyms for the systemic circulation of the lung. In this presentation, two of these—"bronchial circulation" and "pulmonary collateral circulation" will be used interchangeably. It should be emphasized, however, that even though the designation "bronchial circulation" is retained for the sake of convention, the term is inadequate since (1) the systemic arterial vessels to the lung include arteries other than the bronchial arteries, and (2) the systemic arterial blood is distributed to intrapulmonary structures as well as to the bronchi.

It is generally held that as the pulmonary collateral circulation expands it assumes new functions. In figure 2 are illustrated the functions that may be subserved by the normal and by the expanded pulmonary collateral circulations. Precisely which function the expanded circulation will assume depends on two major conditions: (1) the total quantity of blood transported by the pulmonary circulation per unit time, i.e., the combined rates of pulmonary arterial and pulmonary collateral blood flow and (2) the access of hypoxemic collateral arterial blood to the pulmonary alveoli. For example, when the pulmonary arterial blood flow is normal and the systemic arterial blood is well oxygenated, the increment in total pulmonary blood flow contributed by the collateral arterial circulation may constitute a hemodynamic burden (middle panel); on the other hand, when the pulmonary arterial inflow of venous blood is abnormally low and the collateral arteries deliver hypoxemic blood to the alveolar capillaries, the collateral circulation may participate in oxygen uptake (right panel).

It should be noted that the anatomic peculiarities of the pulmonary collateral circula-

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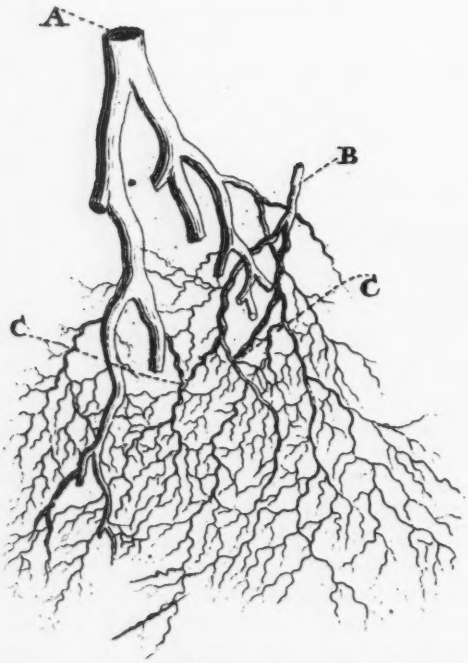


**Figure 1**

*The pulmonary arteries (A) and the bronchial arteries (B) are joined by fine anastomotic channels (C). After Ruysch (1731).*[7]

tion impose severe restrictions on physiologic measurements.[5] For example, the multiple origins of the collateral arterial branches[6] and the alternative outlets of the collateral veins complicate the direct measurement of the collateral blood flow not only in intact animals but in animals with opened chest and exposed heart and great vessels. Nor is it a simple matter to estimate the drop in blood pressure along the course of tortuous anastomotic channels of varying lengths and calibers. On the other hand, the existence of precapillary anastomoses[7-9] does provide the opportunity to measure that part of the collateral arterial inflow that reaches the alveolar-capillary interface and participates in respiratory gas exchange, i.e., the "effective" collateral blood flow.[10, 11] This topic will be considered in detail subsequently.

The remainder of this essay considers the clinical significance of the pulmonary collateral circulation in terms of the three potential functions depicted in figure 2: nutrient, hemodynamic, and respiratory.

### The Pulmonary Collateral Circulation as a Nutrient Circulation

In the normal lung, the collateral arterial circulation satisfies the usual criteria for a nutrient circulation: it is small, it carries oxygenated blood, and its blood is distributed to the walls of the tracheobronchial tree, the supporting framework of the lungs, and the adventitial aspect of the pulmonary arteries and veins.[6]

It seems self-evident that this diminutive circulation lacks the capacity to transport large quantities of blood. This view is consistent with the bulk of the experimental evidence that the normal collateral blood flow is approximately one to two per cent of the cardiac output;[12-15] but, it is contrary to that of I. de B. Daly and co-workers,[5] who found in special preparations that the collateral circulation may exert an appreciable hemodynamic effect on the pulmonary circulation. The apparent inconsistency may lie in the nature of Daly's experiments: their design seems more apt to disclose the ultimate potential of the collateral circulation rather than its usual performance either in vivo or during less drastic experimental circumstances.

The nutrient circulation of the lungs has attracted clinical attention on three counts. The first is the observation that occlusion of either a very large or a very small pulmonary artery by ligation or by an embolus is rarely followed by pulmonary infarction. The viability of the pulmonary tissue in the face of pulmonary arterial occlusion (fig. 3) may logically be attributed to the nutrient circulation.

The second reason for clinical interest (fig. 4) is the hypothesis that obliteration of the nutrient circulation may be involved in the genesis of "ischemic pulmonary disease." A clinical example of a consequence of this disorder would be "emphysema.[16-19] Unfortunately, this plausible hypothesis lacks convic-

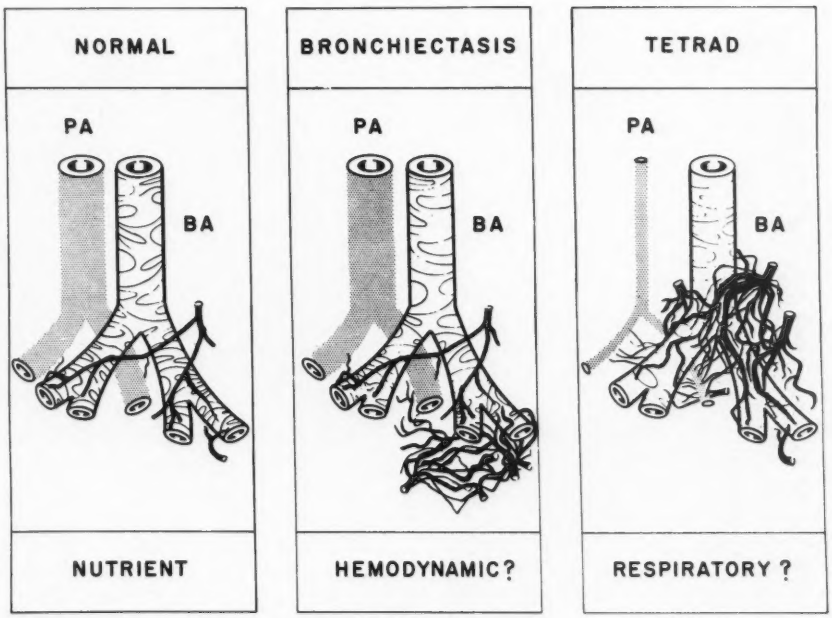


**Figure 2**

*Schematic representation of three potential functions of the systemic arterial blood supply to the lungs. For each function is indicated: (1) the relative sizes of the pulmonary arterial (PA) and the bronchial arterial (BA) circulations and (2) a corresponding clinical state.*

tion on several accounts: (1) the practical difficulty of deciding if a sparse collateral circulation in clinical "emphysema" is the cause, or merely a consequence, of the intrinsic pulmonary disease;[19] (2) the evidence that in some instances of "emphysema," the collateral arterial circulation of the lung may be unusually prominent;[3] (3) the ambiguous use of the term "emphysema" in both clinical and anatomic descriptions; and (4) the uncertainty concerning the relevance of animal experiments in which the pulmonary collateral blood supply of the lung is deliberately compromised, to the various types of "emphysema" encountered in clinical medicine. At the present time, the notion of "ischemic pulmonary disease" is intriguing, but without clinical or experimental substance.

The third reason for clinical interest lies in the demonstration that *primary* carcinoma of the lung—in contrast to metastatic carcinoma—may be deprived of a pulmonary arterial blood supply by thrombosis.[3, 20] An extreme instance of this phenomenon is illustrated in figure 5. In such cases of bronchogenic carcinoma with interrupted pulmonary arterial blood supply, the adjacent bronchial arteries have been found to be unusually prominent.[3, 20] It seems reasonable to implicate the combination of the expanded systemic arterial blood supply and the strategic location of the neoplasm with respect to the tracheobronchial tree in the brisk hemoptysis of patients with bronchogenic carcinoma. Moreover, the blood supply to a pulmonary neoplasm may also determine the success of measures designed to destroy the tumor. For example, the introduction of cancerocidal agents directly into the pulmonary artery for the treatment of a bronchogenic carcinoma presupposes that mixed venous blood has direct access to the tumor;[21] but, as indicated

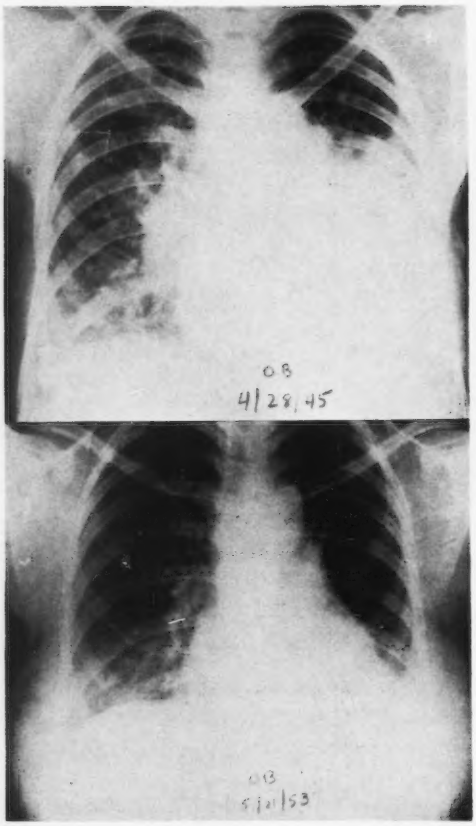


**Figure 3**

*Posteroanterior x-rays of the chest in a young woman (O.B.) prior to (1945), and 8 years after (1953), ligation of the left pulmonary artery. Despite the lack of a pulmonary arterial blood supply, the ventilatory performance of the left lung was virtually unimpaired.*[11]

above, the bulk of the evidence is against this view. Finally, the oxygenation of the blood to a pulmonary tumor may influence not only its pattern of growth but also its response to therapeutic agents.

### The Hemodynamic Effects of the Pulmonary Collateral Circulation

The arterial and venous portions of the pulmonary collateral circulation need not expand proportionately.[22, 23] Moreover, the two vascular segments seem to be stimulated to proliferate by entirely different pathologic processes. Consequently, they are considered separately.

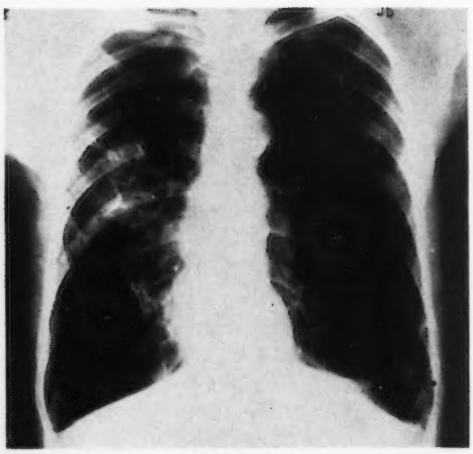

**Figure 4**

*Posteroanterior x-ray of the chest of a 36-year-old man with bullous ("atrophic") emphysema. The patient does not have either chronic bronchitis or other apparent cause for the rarefaction of the lung. The relationship of bullous emphysema to "ischemic pulmonary disease" is unclear.*

Striking enlargement of the collateral *arterial* circulation has been observed both in chronic fibrosing pulmonary disease[24-26] and after ligation of one pulmonary artery.[27-31] In these situations, the normal pulmonary arterial blood flow is supplemented by an increment in blood flow from the collateral arterial circulation. Although some proliferation of the collateral arterial vessels also occurs in the vicinity of healed surgical incisions of the lung and of localized pulmonary lesions such as tuberculosis,[3, 32, 33] bronchiectasis,[24-26] bronchogenic carcinoma,[3] and pulmonary emboli,[1, 29] it seems reasonable to look to the human subjects with *generalized* pulmonary inflammatory disease, and to both dogs and humans with ligated pulmonary arteries for *maximum* hemodynamic effects.

It should, perhaps, first be emphasized that the anatomic display of large collateral arteries provides, per se, no reliable measure of their hemodynamic significance. The uncertainty stems from the lack of information

**Table 1**

*"Effective" Collateral Blood Flow in Twelve Subjects*

| Subject | Diagnosis | "Effective" collateral L./min. | "Effective" collateral / Total × 100 per cent |
|---|---|---|---|
| Permanent occlusion of one pulmonary artery | | | |
| O.B. | 11 Years after ligation | .86 | 8 |
| A.B. | 6 Months after occlusion | 0 | 0 |
| Occlusion of one pulmonary artery by balloon | | | |
| J.S. | Carcinoma | 0 | 0 |
| J.Mc | Carcinoma | 0 | 0 |
| P.C. | Carcinoma | 0 | 0 |
| J.C. | Bronchiectasis | .32 | 4 |
| T.C. | Bronchiectasis | .38 | 4 |
| J.G. | Idiopathic clubbing | .35 | 8 |
| Congenital atresia of main pulmonary artery | | | |
| J.W. | Tetralogy of Fallot | 2.54 | 100 |
| W.Y. | Tetralogy of Fallot | 1.35 | 100 |
| A.K. | Tetralogy of Fallot | 3.79 | 100 |
| B.C. | Tetralogy of Fallot | 5.00 | 100 |

concerning the behavior of the anastomotic channels: do they serve merely as passive conduits between the high-pressure systemic circulation and the low-pressure pulmonary circulation or do they operate, instead, as high-resistance, sphincteric vessels under the control of systemic vasomotor nerves?[5, 12, 14, 34] In favor of the latter view is the sphincteric construction of the collateral arteries[35, 36] as well as the lack of evidence for either left ventricular enlargement or an abnormally wide systemic pulse pressure in patients with enormous overgrowths of the collateral arterial circulation. On the other hand, Alley and co-workers[37] have shown by angiocardiography that in a lung that has been virtually destroyed by chronic suppurative disease, the anastomotic channels do seem to serve as low-resistance conduits, delivering arterial blood into the pulmonary circulation with sufficient force to divert mixed venous blood away from the anastomotic sites. All-in-all, the available evidence suggests that (1) local expansion of the collateral arterial circulation in the vicinity of local pulmonary disease is apt to be without appreciable hemodynamic effect (this conclusion is consistent with the normal pulmonary hemodynamics that characterize multilobar, but circumscribed, bronchiectasis)[11] (2) generalized expansion of the collateral arterial circulation may affect the distribution of mixed venous blood throughout the lung; this situation is apt to obtain in universal bronchiectasis or in generalized, suppurative disease of the lung,[37] and (3) the largest collateral arterial circulations are smaller than many of the left-to-right shunts encountered in congenital heart disease; this conclusion is supported by the lack of left ventricular enlargement and of pulmonary hypertension in patients with large collateral circulation.[11] It should be noted that the inability of the expanded collateral circulation to affect, per se, the behavior of either the pulmonary circulation or left heart does not exclude the possibility of a secondary role, e.g., in aggravating or producing pulmonary hypertension in patients with restricted pulmonary vascular beds.[38]

The appraisal of the hemodynamic significance of an expanded collateral *venous* circulation is still in its infancy. The largest collateral venous circulations have been induced experimentally by ligation of lobar pulmonary veins[39, 40] and occur spontaneously in "emphysema."[22, 23, 38] The general uncertainties that attend the indiscriminate use of the term "emphysema" have been mentioned

**Table 2**

*Relationship between the "Effective" Collateral Blood Flow and Clubbing of the Digits*

| Clinical state | Clubbed digits | "Effective" collateral |
|---|---|---|
| Idiopathic clubbing | + | + |
| Bronchiectasis | + | + |
| Pulmonary congenital atresia | + | + |
| Ligated pulmonary artery | 0 | + |
| Bronchogenic carcinoma | + | 0 |

previously. With particular respect to the collateral venous circulation, the published reports fail to establish if the proliferation of the collateral veins is a regular feature of all types of "emphysema," including the rarefied, destroyed lungs of "chronic bronchitis and emphysema," or only of bullous disease of the lung.

In the normal lung, the proximal bronchial veins drain predominantly into the right atrium.[22, 23] The arrangement of the alternate pathways, which ordinarily favors the drainage of these vessels into the right atrium, is schematically depicted in the left half of figure 6. Liebow[23, 38] has suggested that with the advent of right heart failure, the combination of an elevated right atrial pressure and insufficient bronchial venous valves may re-route the proximal bronchial venous drainage into the left atrium.[23, 38] According to this concept illustrated in the right half of figure 6, right heart failure should be self-perpetuating by virtue of the increased systemic arterial hypoxemia and the pulmonary arterial hypertension which it effects.

Although the proposed increment in bronchial venous return is of conceptual interest, its practical meaning is obscure. A major difficulty in interpretation is the complex interplay of initiating and aggravating factors in hypoxemic types of right heart failure so that quantitative measurements of bronchial venous return to the left heart become exceedingly complicated. Recent advances in respiratory methodology, however, have revived the prospect of separating the increase in *anatomic* venous admixture contributed by the bronchial veins from the *"venous-like"* admixture that results from inhomogeneity of alveolar ventilation and perfusion.

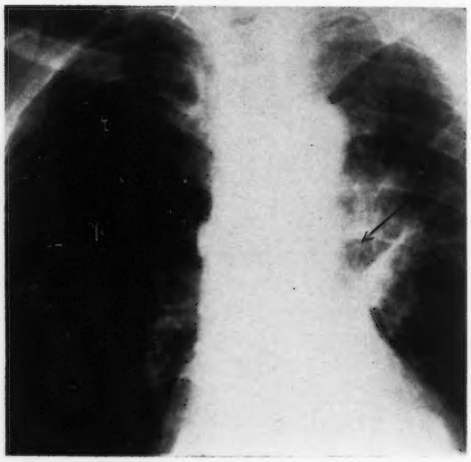

**Figure 5**

*Posteroanterior x-ray of the chest in a man with a bronchogenic carcinoma (arrow), which occluded completely the left pulmonary artery. The complete occlusion was verified by angiocardiography[11] and at autopsy.*

### The Role of the Pulmonary Collateral Circulation in Alveolar-Capillary Gas Exchange

By a series of ingenious and complicated experiments on dogs that had been subjected to ligation of a major pulmonary artery, Bloomer and co-workers[10] showed that the expanded collateral circulation was available, at least in part, to participate in alveolar-capillary gas exchange. Since these experiments involved deep anesthesia, the blood that reached the lung by way of the collateral circulation was unsaturated with oxygen, and could therefore take up oxygen from the alveolar gas.

Unfortunately, such a protocol cannot be applied to the study of unanesthetized animals or man, since their collateral arterial blood, which is normally saturated with oxygen, can take up very little additional oxygen from the alveoli (fig. 7). The spirograms, from the right and left lungs, respectively, were obtained by bronchospirometry from a patient who, in 1946, had undergone urgent ligation

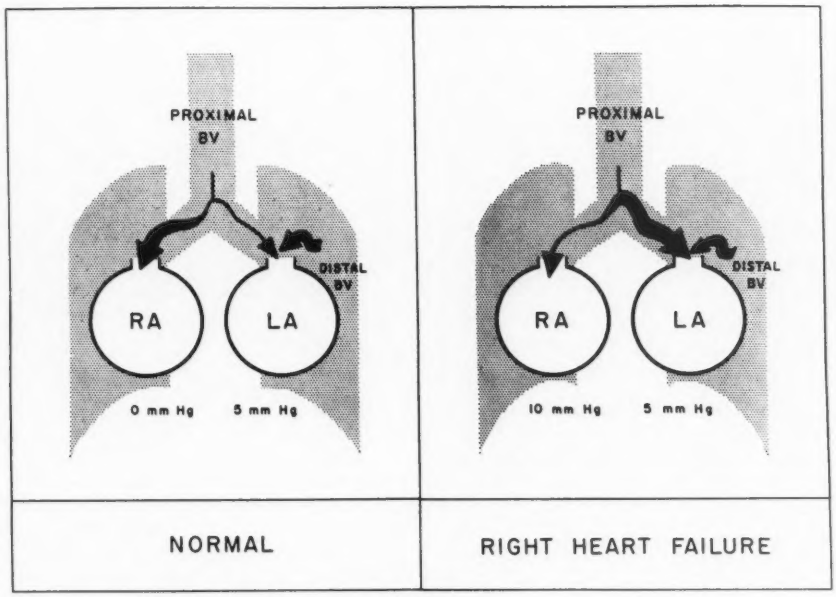


**Figure 6**

*Schematic representation of the collateral venous circulation of the lung. In the normal lung, the proximal bronchial veins are depicted as draining predominantly into the right atrium. With the advent of right heart failure, the proximal bronchial veins are shown emptying predominantly into the left atrium. Based on Liebow[23]*

of the left pulmonary artery during the course of an operation designed to close a patent ductus arteriosus.[41] It may be seen that under ordinary conditions of ambient air breathing, the lung with the ligated pulmonary artery barely contributes to oxygen uptake. The reason for this low oxygen uptake is the small diffusion gradient for oxygen (fig. 8). The effect of improving this diffusion gradient, and the demonstration that the lack of oxygen uptake is attributable to the high oxygenation of the collateral arterial blood rather than to the lack of a precapillary pulmonary collateral circulation, is shown in figure 9. This figure illustrates the use of bronchospirometry to induce collateral arterial hypoxemia while maintaining alveolar oxygen tensions in the left lung, at, or above, ambient air values; under this special circumstance, the oxygen uptake by the left lung increased to approximately 60 ml. per minute, indicating that in man, as in the dog, ligation of a pulmonary artery provokes a proliferation of the collateral arterial circulation.[11]

The experiences with two such patients,[11] as well as with the separate measurement of blood flow through each lung,[42] suggested an experimental approach of wider applicability. In each case, a technic was applied that permitted the use of the Fick principle to measure the rate of "effective" collateral arterial blood flow. This approach required (1) the arrest of pulmonary arterial blood inflow and (2) the perfusion of the pulmonary capillaries by hypoxemic collateral arterial blood (fig. 10). In patients with discrete, unilateral pulmonary lesions, the protocols were complicated; they included (1) bronchospirometry for the administration of different inspired gas mixtures to each lung and for the separate collection of the expired gases; (2) cardiac catheterization for the sampling of mixed venous blood and for the inflation of an occlusive balloon in the pulmonary artery to

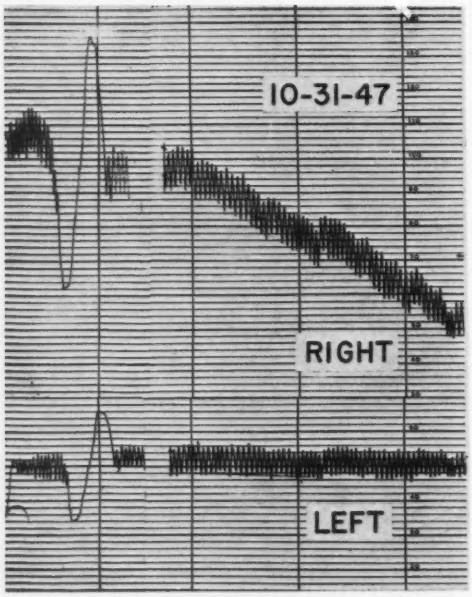


**Figure 7**

*Bronchospirometric record from subject (O.B.), one year after ligation of the left pulmonary artery. The record of oxygen uptake of the left lung shows virtually no slope. A virtually identical record was also obtained in 1956.[11] (Reproduced, in part, with permission from the* Journal of Clinical Investigation)

one lung; and (3) brachial arterial cannulation for the sampling of systemic arterial blood. By way of contrast, in patients whose lungs were perfused solely by systemic arterial blood, e.g., pulmonary atresia (fig. 11), the protocol simply required the measurement of oxygen uptake and the procurement of a blood sample from a peripheral artery.

It should be emphasized that measurements of "effective" flow by the Fick principle, i.e., based on alveolar-capillary gas exchange, can only provide a minimal estimate of the collateral arterial blood flow; by definition, they exclude the "ineffective" flow, i.e., that portion of the total collateral arterial blood flow that bypasses the gas exchanging surface of the lungs. It is also noteworthy that protocols such as those described, which involve the deliberate occlusion of one pulmonary artery,

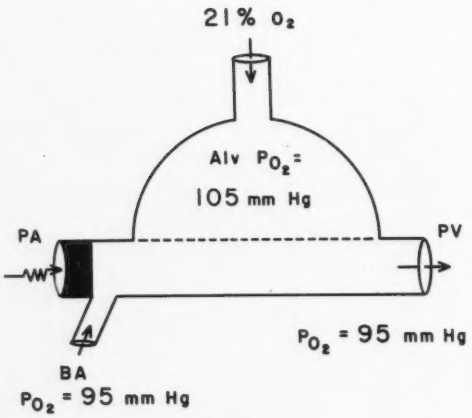


**Figure 8**

*Schematic representation of the diffusion gradient for oxygen in the lung with a ligated pulmonary artery during ambient air breathing. The average difference in oxygen tension along the length of the pulmonary capillary, i.e., 10 mm. Hg is too small for an appreciable oxygen uptake.*

should theoretically augment the collateral flow by decreasing the pulmonary arterial pressure at the outlet of the anastomoses.[12, 34]

The "effective" collateral blood flow was measured in 12 human subjects.[11] The clinical description of each subject is related to the value for "effective" collateral flow in table 1. It may be seen that no "effective" collateral blood flow could be detected either in the normal lung or in the lung that contained a bronchogenic carcinoma. By way of contrast, large "effective" flows—approximating normal pulmonary arterial values at rest (and even increasing somewhat during mild exercise)—were measured in the patients with congenital lack of a pulmonary arterial blood supply.[43] One of these patients, a young woman with limited exercise tolerance, came to autopsy following an attempt to supplement surgically the pulmonary collateral blood flow through the creation of an additional systemic-pulmonary arterial anastomosis. Unfortunately, the sacrifice of her spontaneous pulmonary collateral circulation (fig. 12) during thoracotomy effected a decrease in the pulmonary blood flow that was not offset by the artificial anastomosis.

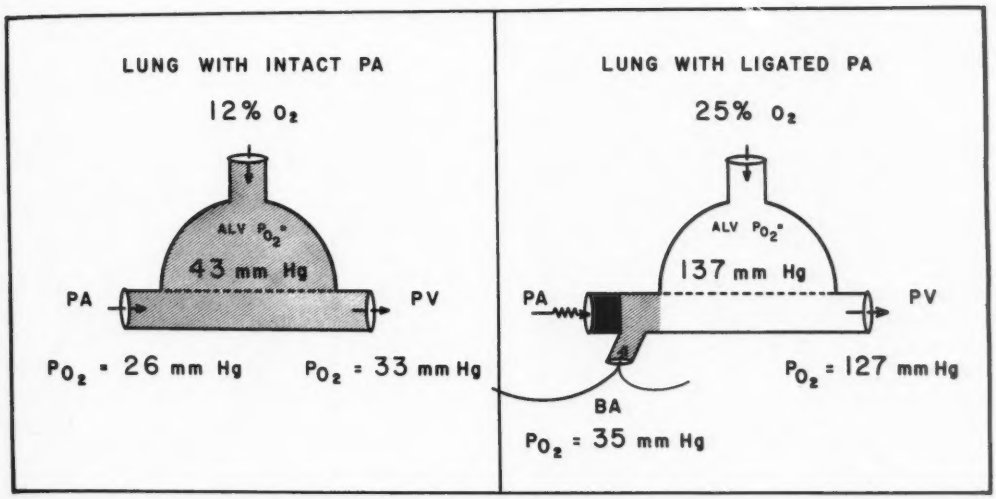


**Figure 9**

*Schematic representation of the diffusion gradient for oxygen in the lung with the ligated pulmonary artery when both lungs breathe different oxygen mixtures. Bronchospirometry is used to (1) induce collateral arterial hypoxemia by administering 12 per cent oxygen to the intact lung and (2) maintain high alveolar oxygen tensions in the lung with the ligated pulmonary artery by administering 25 per cent oxygen to it. As a result of this arrangement, a large diffusion gradient for oxygen exists in the lung with the ligated pulmonary artery.*

### The Role of the Pulmonary Collateral Circulation in the Pathogenesis of Hemoptysis and of Clubbing of the Digits

There is considerable anatomic evidence to suggest that an abnormal pulmonary collateral circulation may be responsible for hemoptysis in a wide variety of cardiac and pulmonary disorders. For example, the expanded collateral *arterial* circulation may be responsible for hemoptysis in patients with tuberculous cavitation,[3] bronchiectasis,[24] and bronchogenic carcinoma.[3, 44] In contrast to the relatively high incidence of hemoptysis in bronchogenic carcinoma, the incidence is low in metastatic carcinoma, which lacks an expanded collateral arterial circulation.[3] The collateral venous circulation is generally held to be a major basis for hemoptysis in mitral stenosis.[45] Another cause for hemoptysis in mitral stenosis is pulmonary infarction, which has been ascribed to an excessive collateral arterial inflow into a vascular segment that has been deprived of its pulmonary arterial inflow by a embolus.[46]

In recent years, evidence has been adduced to implicate the pulmonary collateral circulation in the genesis of clubbed digits in certain clinical disorders.[11, 13, 47, 48] But, that this collateral circulation is not the common denominator in all forms of clubbed digits is easily shown. For example, while certain pulmonary diseases commonly associated with clubbing, i.e., bronchiectasis and bronchogenic carcinoma are generally accompanied by an expanded collateral circulation, other pulmonary diseases, such as tuberculosis, with equally prominent collateral arterial circulations[3] are generally not associated with clubbed digits. Moreover, in clinical states such as subacute bacterial endocarditis, in which clubbed digits are common, prominent collateral circulations remain to be identified. Finally, it is beyond the stretch of the imagination to conceive a role for the pulmonary

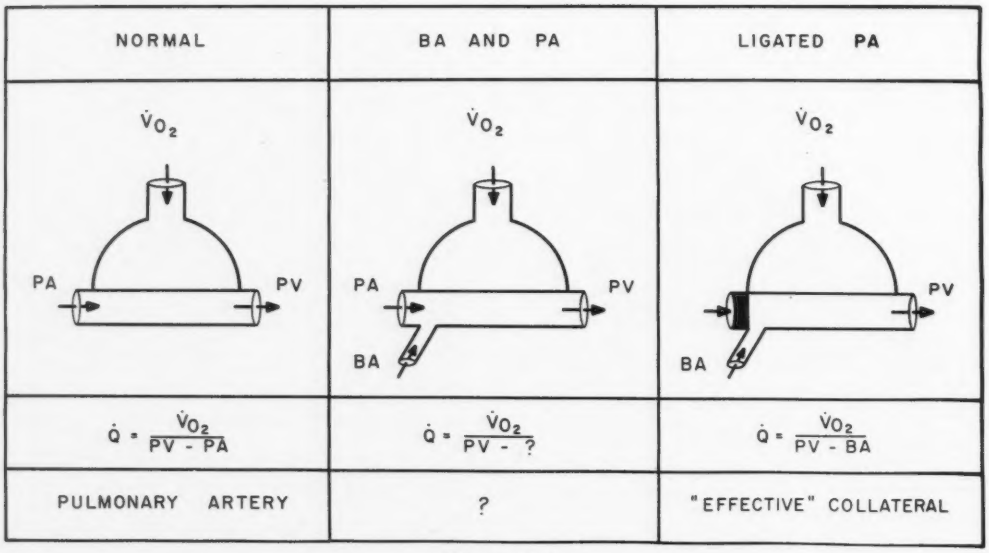


**Figure 10**

*Schematic representation of the use of the Fick principle for the measurement of the pulmonary arterial and the "effective" collateral blood flows. In the middle panel is illustrated the complexity of applying the Fick principle when the pulmonary capillary bed is perfused by both mixed venous and systemic arterial blood. In this anatomic circumstance, the arrest of the pulmonary arterial inflow by an occlusive balloon (right panel) establishes an experimental circumstance for the measurement of the "effective" collateral arterial blood flow.*

collateral circulation in unilateral clubbing.

The possibility that the collateral circulation may, in some instances, be involved in the genesis of clubbed digits has encouraged speculation about which portion of the total collateral arterial inflow could be involved, i.e., the "effective" portion, which participates in alveolar-capillary gas exchange, or the "ineffective" portion, which bypasses the gas-exchanging surface of the lung. Evidence can be mustered from published reports to support either view. Our own experience (table 2) and that of others,[20] would favor the "ineffective" portion. This evidence is predominantly one of exclusion. For example, patient O.B., with the ligated pulmonary artery and a large "effective" collateral blood flow (table 1) had no clubbing of the digits. Similarly, patient A.B. with bronchogenic carcinoma and clubbed digits had no appreciable "effective" flow. On the other hand, the results of others, using more indirect methods, support the view that it is the "effective" rather than the "ineffective" portion of the collateral blood flow that is responsible for clubbing of the digits.[48] These divergent opinions are cited not as a point of departure for resolving a troublesome question, but rather to emphasize that the relationship between clubbed digits and the pulmonary collateral circulation is still an enigma.

### General Comments

Before closing, three other aspects of the pulmonary collateral circulation warrant mention: (1) the limitations of available methodology, (2) the insights that the pulmonary collateral circulation affords into the growth of collateral circulation in general, and (3) the therapeutic implications of the pulmonary collateral circulation.

It is to be anticipated that a full understanding of the clinical significance of the

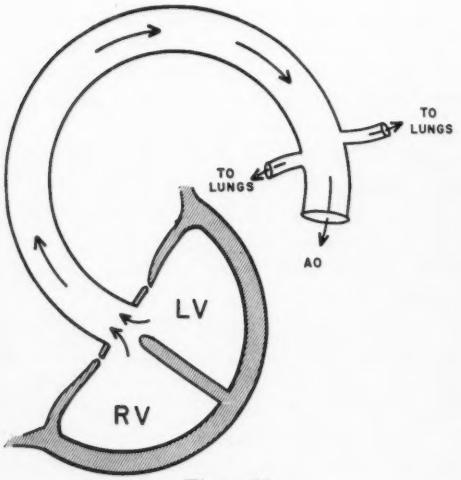


**Figure 11**

*The anatomic basis for measuring "effective" collateral blood flow in subjects with either pulmonary atresia and a ventricular septal defect or truncus arteriosus. Since the total blood supply to the lungs derives entirely from the systemic circulation, the Fick principle is easily applied.*[11]

pulmonary collateral circulation will result from a combination of clinical, physiologic, and anatomic approaches. At the present time, although clinical descriptions may often be inadequate for precise clinicopathologic correlations, and many clinical states remain to be explored by anatomic methods, it is predominantly the physiologic methodologies that are lacking. For example, there is no reliable way, in either intact animal or man, to measure rates of collateral blood flow that are less than 10 to 15 per cent of the cardiac output.[11, 13, 15] The suspicion that lesser flows may be involved in clinical syndromes, e.g., clubbing of the digits, has driven investigators to indirect methods that can only establish qualitatively the presence of collateral arterial inflow into the lungs. These indirect methods have involved the sampling of highly oxygenated blood from diseased portions of the lung and the recording of distorted pressure pulses from diseased regions.[33, 48, 49] But except in instances of flagrant anastomoses—such as in the "destroyed lung"—these measurements are too susceptible to technical limitations and to misinterpretation to inspire confidence.

**Figure 12**

*The pulmonary collateral circulation in a young woman with congenital atresia of the main pulmonary artery. The pulmonary arteries were injected with a light (yellow-green) plastic; the bronchial arteries were injected by way of the aorta with a dark (red) plastic. The sites of confluence of the two systems appear as mixtures of the two shades. (Prepared by Dr. Richard L. Naeye).*

The clinicopathologic studies of the pulmonary collateral circulation have thrown some light on the general principles involved in the development of collateral circulations.[50, 51] For example, Liebow and co-workers have shown that (1) in accord with the observations of Schlaepfer,[31] the pulmonary collateral circulation develops more rapidly in the newborn than in the adult;[4] (2) the decrease in blood pressure beyond the site of pulmonary vascular occlusion is probably a stimulus for the expansion of the collateral circula-

tion;[27] and (3) purely mechanical factors are insufficient to account for the extent or the organization of the expanded collateral circulation.[39, 52] Weibel[53] has extended these studies by demonstrating the sequences of development of the expanded collateral circulation: an initial enlargement of existing vessels followed by a period of angiogenesis. These observations of Schlaepfer, Liebow, and Weibel are all consistent with the demonstration (table 1) that congenital atresia of a pulmonary artery is associated with disproportionately larger pulmonary collateral blood flows than is ligation of a pulmonary artery in adulthood.[11]

Finally, Liebow and co-workers have attempted to turn the pulmonary collateral circulation to therapeutic advantage. They have devised procedures that are designed to relieve myocardial ischemia[54] and to bring oxygenated blood into the aorta of patients with congenital transposition of the great vessels.[52] Up to this time, the practicality of these therapeutic procedures has not been established.

## Summary

The clinical significance of the normal and the expanded pulmonary collateral circulation is considered from the point of view of its nutrient, hemodynamic, and respiratory functions.

In the normal lung, the collateral arterial circulation is too diminutive to serve other than a nutrient function. Its roles in preventing pulmonary infarction after embolization, in producing "ischemic lung disease," and in the direct treatment of pulmonary carcinomas are considered.

The expanded collateral arterial circulation associated with localized pulmonary lesions or which occurs after ligation of a pulmonary artery seems to be without appreciable hemodynamic effect on either the pulmonary circulation, the left heart, or the systemic circulation. Only in patients with generalized suppurative disease of the lung has it been shown to affect the pulmonary circulation by diverting mixed venous blood away from diseased areas. The possibility exists that the increment in pulmonary blood flow contributed by the collateral arterial circulation may aggravate pulmonary hypertension in patients with diffuse restriction of the pulmonary vascular bed.

The venous portion of the expanded collateral circulation may conceivably contribute to pulmonary hypertension by aggravating systemic arterial hypoxemia in patients with right heart failure from hypoxemic cor pulmonale.

The expanded collateral arterial circulation may assume a major respiratory function in subjects with systemic hypoxemia and curtailed pulmonary blood flow. In such cases, the "effective" pulmonary collateral blood flow has been shown to equal normal values for pulmonary arterial blood flow.

Different portions of the pulmonary collateral circulation may be responsible for hemoptysis in different diseases: in pulmonary disease, the arterial portion; in mitral stenosis, the venous portion; in pulmonary infarction, an imbalance between the two.

The relationship between the pulmonary collateral circulation and clubbing of the digits remains uncertain.

The pulmonary collateral circulation is considered, finally, with respect to (1) limitations of present methodology, (2) principles involved in the development of collateral circulations in general, and (3) therapeutic implications.

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Laennec's contributions to the study of diseases of the lungs, of the heart, and of the abdominal organs really laid the foundation of modern clinical medicine.—SIR WILLIAM OSLER. *Aphorisms from His Bedside Teachings and Writings.* Edited by William Bennett Bean, M.D. New York, Henry Schuman, Inc., 1950, p. 112.

# ABSTRACTS

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## PATHOLOGY

**McGill, H. C., Jr., Strong, J. P., Holman, R. L. and Werthessen, N. T.: Arterial Lesions in the Kenya Baboon.** Circulation Research **8**: 670 (May), 1960.

Findings at necropsy on a 16-year-old female baboon that died of infection in a North American zoo revealed many atheromata in the lower part of the abdominal aorta, similar to the lesions of atherosclerosis in the human. Because baboons may have a higher incidence of atherosclerosis than had been suspected for most primates and because these lesions may develop in the absence of excessive dietary cholesterol, a study was undertaken to determine the precise incidence of arterial lesions in baboons that had lived in their natural habitat. Study was made of 163 such animals immediately after they were trapped in Kenya, British East Africa. Some deposition of lipid was found in the intima of the aorta in approximately three fourths of the 67 adults, and this was extensive in a few animals. No sex difference was observed. Electron microscopy disclosed that most of the lipid droplets in the intima were intracellular. Fibrous plaques were infrequent. However, in one elderly male they were noted, and hemorrhage had occurred into the bases of the plaques. Sections of coronary arteries showed many small musculo-elastic intimal plaques in which lipids could be demonstrated only rarely. The aortic lesions occurred in the absence of excess intake of animal fat or hypercholesteremia. It was suggested that the baboon is highly susceptible to lipid deposition in the arterial intima and, therefore, that it will lend itself well to the experimental study of atherosclerosis.

SCHIRGER

**Robertson, J. H.: The Influence of Mechanical Factors on the Structure of the Peripheral Arteries and the Localization of Atherosclerosis.** J. Clin. Path. **13**: 199 (May), 1960.

The peripheral arteries of 81 subjects, ranging in age from 1 month to 95 years, were examined at necropsy. No hypertension was evident clinically or at necropsy in the group. The radial artery at the wrist was examined in 65 cases, and segments obtained from the brachial artery, the upper third of the femoral artery, from the popliteal artery, and from the posterior tibial artery. Three changes were seen to occur in the structure of the peripheral vessels during the first two decades of life. During the first decade the only change observed was some increase in size of the muscular cushions previously observed in the popliteal and lower end of the brachial artery of the fetus. By the end of the second decade further cushions had formed at the mouths of branches in other peripheral vessels, particularly the femoral artery. These cushions were less prominent in the radial and posterior tibial arteries. Simultaneously, with the development of

cushions, bands of longitudinal muscle developed in the brachial and popliteal arteries. At the end of the first and in the second decade the internal elastic lamina began to split to form the muscular elastic layer of the intima. Muscle cells could be observed passing from the media into the newly formed musculo-elastic layer through openings in the internal elastic lamina. The third and later decades were characterized by the development of the elastic hyperplastic layer of the intima and by regressive changes in the muscular cushions and media of the peripheral vessels. Simultaneously, progressive fibrosis of the media with atrophy of its longitudinal muscle occurred. It was suggested that the muscular cushions in the peripheral arteries showed good correlation with the severity of pulsatile stress. In vessels with marked pulsations cushions developed earlier than in the small arteries where the pulse wave was flattened and less steep. The development of the musculo-elastic layer of the intima was thought to occur in response to a gradual rise of the blood pressure throughout life. The authors stated their belief that the development of the musculo-elastic layer of the intima represented hypertrophy of the circular muscle of the vessel in the same way that the fetal cushions represented local hypertrophy of the longitudinal muscle. It was believed that the muscular cushions of the fetus and the later development of the peripheral arteries noted in the study confirmed the presence of pulsatile stress and indicated its importance in the localization of intimal plaques.

SCHIRGER

**Rossi, L., and Levy, A.: Morphologic Anomalies of the Right Branch of the Bundle of His in Cardiac Hypertrophy.** Arch. mal. coeur 53: 154 (Feb.), 1960.

Histologic study of four hearts with predominant left ventricular hypertrophy showed that in three of these, the initial subendocardial portion of the right bundle-branch was shortened while in one heart it was completely missing, the branch showing an intramyocardial course from the beginning. These changes were in direct relation with the degree of ventricular septal hypertrophy.

LEPESCHKIN

**Sheeha, H. L., and Davis, J. C.: Experimental Obstruction of Renal Veins.** J. Path. & Bact. 79: 347 (Apr.), 1960.

Gross and histologic observations were made on the rabbit kidney after various degrees of obstruction of venous outflow were produced. The degree and duration of partial obstruction were varied with production of different degrees of enlargement of the anastomotic channels and thus different grades of renal damage were produced. Necrosis occurred in the tubules in the outer part of the cortex, in the inner intermediate zone of the cortex, and in the outer medulla; no correlation could be made between the lesions in the various zones. Large mononuclear cells were found in the sinuses of the intermediate zone and in the lumen of the cortical veins; these were presumed to be endothelial or monocytic cells that had been washed free into the lumen by the flow of interstitial fluid, which occurred immediately post mortem.

KARPMAN

**Strandness, D. E., Jr., Nothstein, D. L., Alexander, J. A., and Bell, J. W.: Observations on Arteriolar Disease in Arteriosclerosis Obliterans.** Surgery 47: 963 (June), 1960.

Fifteen extremities amputated for complications of arteriosclerosis obliterans and one from a case of thromboangiitis obliterans were studied for arteriolar disease. The Schlesinger radiopaque injection mass was used. Sections for histologic study were taken from major arteries, and additional sections included skin, subcutaneous tissue, and muscle. Sections were taken from four autopsy cases for controls. All patients were normotensive. Eight patients had diabetes mellitus. Major arteries were frequently occluded in several areas. This was generally more extensive among the patients with diabetes mellitus. The arterioles in the 40- to 150-micron range were given special attention. All the limbs showed alterations in these vessels. Those located in the dermis and generally in the more distal areas showed the greatest number of arteriolar changes. Proliferative changes were seen in thick walled vessels—the adventitia and the intima were thickened while the media was thinned. Some arterioles also showed hyaline changes. These usually showed a smaller lumen but occasionally the lumen appeared increased in relation to the wall thickness. The media sometimes showed no smooth muscle. The changes were classified as severe in two cases, moderate in eight, and minimal in five. The case of thromboangiitis obliterans did not show hyaline or proliferative changes. The patients with diabetes mellitus did not differ. The authors comment that these changes are similar to those described as being the basis for hypertensive ischemic ulceration although these subjects were normotensive. It is postulated that involvement of the arteriolar bed may so greatly increase the resistance to blood flow as to compromise the results of angioplastic procedures and lumbar sympathectomy.

SHEPS

## PHARMACOLOGY

**Cass, R., Kuntzman, R., and Brodie, B. B.: Norepinephrine Depletion as a Possible Mechanism of Action of Guanethidine (SU5864), A New Hypotensive Agent.** Proc. Soc. Exper. Biol. & Med. 103: 871 (Apr.), 1960.

The authors injected rabbits with SU5864 (guanethidine), 12.5 mg. per Kg. intravenously, and cats, 15 mg. per Kg. subcutaneously. They found that in both animals the SU5864 lowered the norepinephrine level of the heart and spleen, but did not effect the norepinephrine level of the brain or adrenal medulla. The failure of guanethidine to lower the content of brain norepinephrine level was believed to be due to its extremely low lipid solubility and, hence, its difficulty in crossing the blood-brain barrier. These findings suggest that guanethidine acts as a hypotensive agent by producing a chemical sympathectomy through depletion of norepinephrine from peripheral nerve endings. However, the catecholamine depletion observed after guanethidine is slower than after reserpine.

KRAUSE

**Gvozdjak, J., Niederland, T. R., and Somodska, V.: The Extracardial Effect of Digitoxin on the Carbohydrate Metabolism of the Organism.** Cor et Vasa 1: 161, 1959.

Rats receiving daily doses of digitalis in ethanol showed a steep decline of free glycogen in the liver and in skeletal muscle, persisting during the entire experiment. This decline was present also in animals receiving only the solvent, but it was not as pronounced as in animals receiving digitalis. Bound glycogen in skeletal muscle did not show significant changes, while in the liver it persisted on a lower level throughout the experiment; these changes were less pronounced than those of free glycogen.

LEPESCHKIN

**Gvozdjak, J., and Somodska, V.: Dynamic Investigation of the Effect of Digitoxin on the Glycogen Content of the Myocardium.** Cor et Vasa 1: 156, 1959.

White male rats that received a daily dose of 0.4 mg. per 100 Gm. of digitoxin dissolved in ethanol intraperitoneally and were killed on the first to sixth day of the experiment showed a statistically significant increase of free myocardial glycogen during the first 2 days as compared with animals that received only the solvent.

LEPESCHKIN

**Havard, C. W. H., and Wood, P. H. N.: Clinical Evaluation of Benzthiazide, an Oral Diuretic.** Brit. M. J. 1: 1773 (June 11), 1960.

The action of benzathiazide was compared with that of chlorothiazide. The drugs were first tried on two young men in good health who were hospitalized for investigation of minute tuberculous foci. Both men had relatively similar food and fluid intakes and a similar electrolyte pattern. Observations were made before and after the administration of the drugs, benzathiazide being given in a 100-mg. dose and chlorothiazide in a dose of 1 Gm. Urine volume with both drugs reached maximum excretion within 6 hours and returned to control levels within 10 hours. Electrolyte excretion ran parallel to water excretion with both drugs, but benzathiazide caused a greater loss of the chloride ion. Chlorothiazide led to excretion of alkaline urine in the first 6 hour period, while benzathiazide produced little alteration in either pH or titrable acidity. Benzathiazide minimally affected bicarbonate excretion, but chlorothiazide greatly increased bicarbonate excretion in the first 6 hours. The drugs were then tried on 15 hospitalized patients of whom nine were in cardiac failure and six had cirrhosis. In the cardiac patients both drugs were equally effective and produced similar results. Four patients responded well with weight loss of 12 pounds during 8 days of therapy. The other five did not do so well, losing an average of only 1.5 pounds during the same period. These five had been on diuretics and low-sodium diets for a long period of time. However, in all patients benzathiazide caused a greater chloride loss than sodium, whereas chlorothiazide tended to cause equal excretion of both sodium and chloride. Potassium loss was the same with both drugs. There was no disturbance of serum electrolytes with either drug and blood urea levels were reduced after treatment with both drugs. No gastrointestinal, hepatic, or hematologic disturbances were observed with use of either agent. Among the cirrhotic patients only 1 had a good response and this patient was the individual in whom sodium excretion during the control period exceeded the dietary intake. The authors believe that benzathiazide, 100 mg., is a good oral diuretic as compared with chlorothiazide, 1 Gm., the biggest difference being in bicarbonate excretion.

KRAUSE

**Kennedy, A. C., Buchanan, K. D., and Cunningham, C.: The Diuretic Activity of Bendrofluazide.** Lancet 1: 1267 (June 11), 1960.

Bendrofluazide is a benzothiadiazine derivative with greater potency than either hydrochlorothiazide or hydroflumethiazide. Volumetric and

biochemical studies of its action were performed in 19 edematous patients and two healthy subjects. Optimal dosage in most patients was 7.5 mg. Maximum diuresis was in the first 12 hours and still appreciable in the second 12 hours. Urinary sodium and chloride were both greatly increased; maximum water diuresis was closely related to them in time. Potassium excretion was increased but to a lesser extent than that of sodium or chloride. Plasma levels of sodium, chloride, and urea showed no change after a single dose, but there was a slight fall in plasma potassium. No toxic effects were noted.

KURLAND

**Keyl, A. C., Suker, J. R., Wessel, H. U., and Rhoads, P. S.: Digitalis Antagonism.** Arch. Int. Med. **105**: 709 (May), 1960.

In a previous paper by the authors digitalis antagonism by potassium salts was discussed. In the dog at rather low levels of K-strophanthin intoxication, potassium in the form of any of its soluble salts appeared capable of reversing electrocardiographic evidence of toxicity. At higher levels of toxicity, however, only the L-glutamic and A-keto glutamic acid salts retained this antidotal property. Actual quantitation of digitalis intoxication was impossible, but an empiric approach by the authors permitted differentiation into "acute" and "subacute" high-level digitalis intoxication in animals. On the basis of these experiments clinical trial of monopotassium glutamate as an antagonist against digitalis intoxication seemed warranted. The drug appeared to be safe even in the presence of altered renal function. Furthermore, correction of electrocardiographic abnormalities due to excess digitalis occurred at the low dose levels of 10 mEq. of potassium. This study confirmed the fact that monopotassium glutamate appears to be just as effective in human as it is in animal digitalis intoxication.

KRAUSE

**Levine, R. R.: The Physiological Disposition of Hexamethonium and Related Compounds.** J Pharmacol. & Exper. Therap. **129**: 296 (July), 1960.

The physiologic disposition of hexamethonium and certain similar compounds was studied in animals. Absorption was poor from the small intestine. There was no biotransformation in the intact mouse. Hexamethonium was found in the blood for an hour following an intravenous dose of 30 mg. per Kg. and was distributed rather uniformly to all tissues including muscle and some adipose tissue depots, but not brain tissue. Following an oral dose, about 40 per cent of hexamethonium was excreted in the urine within 5 hours. Biliary excretion does not represent the major pathway of elimination.

SHEPS

**Mayer, S. E., and Moran, N. C.: Relation between Pharmacologic Augmentation of Cardiac Contractile Force and the Activation of Myocardial Glycogen Phosphorylase.** J. Pharmacol. & Exper. Therap. **129**: 271 (July), 1960.

The contractile force of the heart was measured directly with the strain-gage arch in open-chest dogs with intact circulatory systems. Phosphorylase activity was analyzed from small samples of myocardium cut from the contracting heart "in situ." The positive inotropic effect of epinephrine, norepinephrine, Isoproterenol, Ephedrine, and stimulation of the cardiac sympathetic nerves was accompanied by augmentation of enzyme activity. Methoxamine affected neither contractile force nor phosphorylase activity, while naphazoline produced small increases in force with no change in enzyme activity. Other agents with positive inotropic action (ouabain, theophylline, serotonin, and phenoxybenzamine), had no effect upon the enzyme. Calcium in large doses augmented phosphorylase. Dichloroisoproterenol prevented both the positive inotropic and phosphorylase-activating effects of epinephrine and sympathetic nerve stimulation. Phenoxybenzamine blocked the vasopressor effect of epinephrine, but failed to prevent either physiological or biochemical stimulation of the heart. Pretreatment with reserpine prevented the positive inotropic and the phosphorylase-activating effects of cardiac sympathetic nerve stimulation but did not alter the effects of epinephrine. This was presumably through the mechanism of depleting cardiac catecholamines. It was not possible to decide which was the primary event in the action of catecholamines on the heart—the effect on phosphorylase or on the contractile mechanism—or whether both were concomitant phenomena with no immediate causal relationships.

SHEPS

**Moore, J. I., and Swann, H. H.: Sensitization to Ventricular Fibrillation. I. Sensitization by a Substituted Propiophenone, U-0882.** J. Pharmacol. & Exper. Therap. **128**: 243 (Mar.), 1960.

Alpha-phenoxy-alpha-dimethylaminomethyl propiophenone hydrochloride (U-0882) when administered intravenously in an anesthetized animal, produces a transient depressor effect and concomitant stimulation of respiration. The electrocardiogram and direct measurements show that

the refractory period of the ventricular myocardium is greatly prolonged without depressing intracardiac conduction. This compound is also a weak atropine-like blocking agent. Ventricular fibrillation is easily induced by a subsequent intravenous injection of epinephrine, levarterenol, isoproterenol, or electrical stimulation of the right atrium, the right ventricle, or the stellate ganglion. In the unanesthetized dog, the administration of this compound intravenously produces spontaneous ventricular fibrillation. U-0882-epinephrine fibrillation is not prevented by dibenzylene, quinidine, procaine amide or functional hepatectomy—measures which protect against hydro-carbon-epinephrine fibrillation. Previous administration of toxic doses of Ouabain or dichloroisoproterenol will prevent fibrillation from U-0882. The authors suggest that ventricular fibrillation is a state of continuous conduction and not a state of increased ventricular automaticity. The maintenance of fibrillation depends upon continuous conduction of one or more impulses in relatively refractory tissue. The authors present evidence against the existence of an "excitable gap."

SHEPS

**Moore, J. I., and Swan, H. H.: Sensitization to Ventricular Fibrillation. II. Sensitization by Amarine and Congeners of U-0882.** J. Pharmacol. & Exper. Therap. **128**: 253 (Mar.), 1960.

The action of Amarine and 10 congeners of U-0882 were studied. Like U-0882, Amarine prolongs atrial and ventricular refractory periods and sensitizes the heart to ventricular fibrillation; but Amarine differs in that it has more depressant action upon intracardiac conduction and does not block vagal slowing of the heart or the depressor response to metha-choline. Sensitization to ventricular fibrillation was shared by the three congeners of U-0882 that, like the parent compound, have a keto oxygen and an alpha methyl group. The remaining congeners do not sensitize but produce death by circulatory collapse without ventricular fibrillation.

SHEPS

**Ripka, O., Malis, F., Teichmann, V., and Drab, K.: The Clinical Pharmacology of Dimecamine, a New Oral Ganglion Blocking Agent.** Cor et Vasa **2**: 130, 1960.

Dimecamine (3-dimethylaminoisocamphane), a derivative of mecamylamine, in a single dose of 2.5 to 10 mg. causes a maximum fall of blood pressure in 1 to 2 hours, this low level being maintained for some 12 hours. With subcutaneous administration, 85 to 90 per cent of this dose was excreted with the urine in 4 days, while with oral adminstration this percentage was 62 to 76 per cent. Simultaneous administration of ammonium chloride accelerated the rate of excretion slightly, streptomycin slowed it slightly, while diamox and especially chlorothiazide slowed it considerably. Therapeutic doses were given to 47 patients with hypertension over a period of 12 to 18 months, after a single test dose. This resulted, in most patients, in a marked fall in blood pressure, systolic pressure being affected more than diastolic pressure. A single dose of dimecamine did not cause a decrease in renal blood flow or in glomerular filtration rate, and no renal damage resulted from long-range treatment with the drug. The most serious side effect was constipation, which appeared in 31 patients and resulted in ileus in one. Constipation was most marked in persons who already had such a tendency before treatment, and could be counteracted by synthostigmine but not by conventional laxatives.

LEPESCHKIN

**Ross, J., Jr., Braunwald, E., and Waldhausen, J. A.: Studies on Digitalis. II. Extracardiac Effects on Venous Return and on the Capacity of the Peripheral Vascular Bed.** J. Clin. Invest. **39**: 937 (June), 1960.

Acetylstrophanthidin was administered to dogs previously placed on an extracorporeal pump-oxygenator and the extracardiac vascular effects of the drug were measured. When the portal circulation was kept intact, a decrease in the venous return and intravascular pooling of blood occurred. If pooling in the splanchnic bed was prevented, a decrease in intravascular volume and an increase in venous return occurred. Elevations were noted in the pressures of both the superior and inferior venae cavae. The authors concluded that the hemodynamic alterations produced by digitalis are secondary to peripheral as well as inotropic actions.

KARPMAN

**Schoepke, H. G., and Shideman, F. E.: Cardiac Actions of a Series of Saturated and Unsaturated Bis-trimethylammonium Compounds.** J. Pharmacol. & Exper. Therap. **129**: 322 (July), 1960.

Hexamethonium has previously been demonstrated to exhibit positive inotropic responses without muscarinic activity. In order to correlate structure and activities, other bis-trimethylammonium compounds were studied on the isolated atria of the cat, rat, and on the heart-lung preparation of the dog. A series of alkane, alkene,

and alkyne bis-trimethylammonium compounds was examined. All lacked ganglion-stimulating properties. In contrast, the saturated compounds exhibited little or no inotropic or chronotropic activities. Unsaturation, as well as an increase in internitrogen chain length from C4 to C5 or C6, enhanced cardioinhibitory activity. This was maximum when the internitrogen hydrogen chain contained five or six carbon atoms and a triple bond in the 2,3-position. When the triple bond in the C6 alkyne compounds was moved from the 2,3- to the 3,4-position, there was decreased cardioinhibitory activity. A difference in receptor sites for the inotropic and chronotropic responses was suggested by the observed differences in dose-response relationships, and because negative inotropic activity was greater than negative chronotropic activity in the entire series of unsaturated compounds. Since there was no correlation between internitrogen distance and the observed differences in activities of the compounds, it was postulated that the differences might be related to the effect of the position of the unsaturated group on the reactivity of the nitrogen atom of the quaternary groups.

SHEPS

**Smith, A. M., Jr., and Custer, R.: Toxicity of Vitamin K: Induced Hypoprothrombinemia and Altered Liver Function.** J. A. M. A. 173: 502 (June 4), 1960.

Medical literature is virtually devoid of data relating to toxic effects of vitamin K. Free use of this vitamin, and its analogues, in greater than adequate doses and continued over long periods, may harm the patient, especially the one with hypoprothrombinemia due to a seriously diseasead liver; a condition that cannot be corrected by vitamin K. An 80-year-old woman, admitted for surgery, was found to have a prothrombin time of 18 seconds (40 per cent). She was given 150 mg. of menadiol sodium diphosphate intramuscularly and 50 mg. of phytonadione intravenously. An abdomino-perineal resection performed the next day was uneventful and the liver was grossly normal to inspection. Vitamin K was continued for 11 days (menadiol sodium diphosphate, 30 mg. intramuscularly daily supplemented by 50 mg. of phytonadione by vein on the eighth day through the eleventh) although her prothrombin time had reached the normal of 13 seconds (100 per cent) on the fourth postoperative day. Subsequently there was a fall in prothrombin activity to 29 per cent of normal on the twelfth postoperative day and an increasing hemorrhagic ooze from the wound. Transfusions of fresh blood and discontinuance of vitamin K resulted in improvement. The prothrombin time returned to normal in 3 weeks, but liver-function studies were abnormal for more than a month.

KITCHELL

**Stanton, H. C., and Woodhouse, F. H.: The Effect of Gamma-amino-N-Butyric Acid and Some Related Compounds on the Cardiovascular System of Anesthetized Dogs.** J. Pharmacol. & Exper. Therap. 128: 233 (Mar.), 1960.

Gamma-amino-N-Butyric Acid (GABA) has been obtained from extracts of mammalian central nervous system. This has been reported to possess significant cardiovascular activity. This amino acid and similar compounds were studied. GABA, beta-alanine, 5-amino-N-valeric acid, taurine, sodium butyrate, and butylamine induced a transient, dose-related, blood pressure fall when administered intravenously to anesthetized dogs. Respiratory stimulation was observed following GABA, beta-alanine, and 5-amino-N-valeric acid. GABA also produced a transient pressor response and bradycardia preceding the depressor response. A more prolonged depressor response was occasionally observed following large doses of 6-amino-N-caproic acid, 8-amino-N-caprylic acid, and butalymine. The latter agent also elicited a more transient dose-related depression of blood pressure. Tachyphylaxis to this prolonged blood pressure fall was observed. There was a 25 to 30 second latent period before the response was manifest. The depressor responses induced by GABA were antagonized by beta-alanine, 5-amino-N-valeric acid, and 6-amino-N- capronic acid. It is suggested that in dogs the depressor response induced by GABA may be due in part to peripheral autonomic ganglionic blockade. The pressor and respiratory stimulation induced by this compound may be due to carotid and aortic chemoreceptor stimulation.

SHEPS

## PHYSICAL SIGNS

**Alzamoro-Castro, V., and Battilana, G.: The Double Femoral Sound.** Am. J. Cardiol. 5: 764 (June), 1960.

Coupled sounds were heard over the femoral vessels in eight patients with congestive heart failure of various causes, and case summaries of four of these are presented along with phonocardiograms. In one patient, a 30-year-old woman with idiopathic pulmonary hypertension, the first femoral sound varied in position according to the length of the P-R interval; following a ventricular premature beat, only one sound occurred. In another patient the double femoral sound disappeared when atrial fibrillation developed. It was concluded that the first sound resulted from a powerful right atrial contraction consequent to

disease of the right heart and transmitted to the femoral vein, and that the second sound was produced by left ventricular systole and transmitted to the femoral artery.

ROGERS

**Nixon, P. G. F., Wooler, G. H., and Radigan, L. R.: The Opening Snap in Mitral Incompetence.** Brit. Heart J. **22**: 395 (June), 1960.

The authors reviewed 30 patients with loud opening snaps associated with a pansystolic murmur attributed to mitral regurgitation. In 12 patients the valve was examined at operation; in all instances the aortic cusp was found to be pliant and mobile whereas regurgitation was caused by shrinkage of the mural cusp. A mitral diastolic murmur of variable duration and intensity was heard in all patients. In this series the opening snap did not appear to depend upon the degree of mitral stenosis or the mobility of the mural cusp but rather upon a pliant aortic cusp moving rapidly under the influence of a high left atrial pressure. The patients with dominant regurgitation usually had a third heart sound, left ventricular thrust, and the explosive onset of the diastolic murmur. The authors believed that they could distinguish the latter group, those patients with pliable aortic cusps who would, therefore, be amenable to present-day surgical procedures.

KALMANSOHN

## PHYSIOLOGY

**Bogdonoff, M. D., Weissler, A. M., and Merritt, F. L.: The Effect of Autonomic Ganglionic Blockade upon Serum Free Fatty Acid Levels in Man.** J. Clin. Invest. **39**: 959 (June), 1960.

Serum free fatty acid levels were followed before, during, and after the infusion of saline in one group of patients, and after infusions of Arfonad in a second group of patients. There was a gradual and sustained rise in free fatty acid levels during the saline infusion; in addition, the blood pressure increased although the heart rate and blood sugar values did not change. Ganglionic blockade (with Arfonad) resulted in a fall of free fatty acid levels during the infusion with a sharp rise after infusion; during ganglionic blockade, the blood pressure decreased, with a secondary increase in the pulse rate, and the serum glucose remained unchanged. Ganglionic blockade inhibited the rise of free fatty acid levels following presentation of a threatening stimulus. The authors concluded that the autonomic nervous system provides a stimulatory component to lipid mobilization and that the mechanism is operative in the resting and in the stimulated individual.

KARPMAN

**Burn, J. H.: The Cause of Fibrillation.** Brit. M. J. **1**: 1379 (May 7), 1960.

The history of previous investigations on the mechanism of cardiac fibrillation is reviewed. The circus theory of Lewis, which remained unchallenged for 30 years, is cited. Also described is the production of fibrillation in the dog heart during vagal stimulation and applying a single shock early in the relative refractory period (the vulnerable period). The works of Scherf and Prinzmetal, individually with different technics, are described in support of atrial fibrillation originating from, and perpetuated by, a single rapidly discharging ectopic focus. The combination of an infusion of acetycholine and rapid stimulation produced fibrillation in the atria but not in the ventricles. Since acetylcholine shortens the action potential of the atria, but not the ventricles, this is probably an important mechanism for the production of atrial fibrillation. When the atria are fibrillating due to this procedure and the infusion of acetylcholine is stopped, the atrial fibrillation stops. In fibrillation the muscle fibers are not contracting simultaneously and are out of phase. When a muscle fiber contracts, excitation spreads to adjacent fibers, which will also contract if they are excitable. In the presence of acetylcholine, muscle fibers are rapidly repolarized and after contracting are promptly re-excited so long as the acetylcholine keeps the action potential and the refractory period short. In addition to a short refractory period, the muscle fibers must be out of phase, in order to produce fibrillation. This occurs with rapid stimulation electrically, or can be produced by a rapid stream of impulses by applying aconite. The long refractory period (or the long action potential) of cardiac muscle as compared with that of skeletal muscle protects the cardiac muscle from fibrillation. Energy is required to maintain its length, since, when there is lack of oxygen or glucose, or in the presence of metabolic inhibitors, the action potential is shortened and fibrillation is facilitated.

KRAUSE

**Burns, J. H., and Rand, M. J.: The Relation of Circulating Noradrenaline to the Effect of Sympathetic Stimulation.** J. Physiol. **150**: 295 (Feb.), 1960.

The threshold strength of electrical stimuli on the lumbar sympathetic chain in the intact dog

and in perfused preparations were measured by studying vasoconstrictive phenomena plethysmographically in the intact animal while changes in arterial resistance and venous outflow were measured in the perfused preparations. An infusion of norepinephrine reduced the threshold of sympathetic stimulation (after the direct effect had abated), whereas epinephrine had little or no effect. The authors suggest that at the postganglionic sympathetic nerve ending there is a mechanism for taking up circulating norepinephrine as well as for releasing it. They hypothesize that the norepinephrine secreted into the blood by the adrenal gland replenishes the stores at the sympathetic nerve ending and that if the secretory activity of the adrenal medulla is excessive, the tone maintained by the sympathetic impulses may also be excessive. Furthermore, the disappearance of norepinephrine from the blood may be partly due to its uptake and storage and not due to its destruction.

KARPMAN

**Condorelli, S., and Ungari, C.: The Period of Functional Closure of the Foramen Ovale and the Ductus Botalli in the Human Newborn.** Cardiologia **36:** 274, 1960.

The existence of a physiologic communication through the foramen ovale and through the ductus arteriosus was demonstrated in the newborn infant by means of dye-dilution curves. Communication through the foramen ovale occurs from right to left and the blood passing in that direction comes from the inferior vena cava. Closure of the foramen may take place early (within the first 6 hours of life) or late (more than 8 days after birth). Communication via the duct is left to right. Functional closure of the duct may be early (in the first 6 hours) or late (more than 14 days after birth). Crying, which produces rapid variations in pressure in the right atrium, can activate a right-to-left shunt through the foramen ovale that is not present in the resting state.

BRACHFELD

**de Crinis, K., Redisch, W., Fontana, V., Lewis, A., Sulzberger, M. B., and Steele, J. M.: Vascular Responses to Smoking Tobacco Compared with Responses to Skin Testing of Tobacco Extracts.** Ann. Int. Med. **52:** 1035 (May), 1960.

Eighty healthy subjects were studied to determine the effect of cigarette smoking on blood flow, surface temperature, blood pressure, pulse rate, ballistocardiogram, and electrocardiogram; the same subjects were skin tested with each of the various tobacco extracts. Forty-seven and a half per cent revealed changes in at least one of the circulatory measurements; 40 per cent showed a positive skin test to the tobacco extracts; of the 48 subjects with negative skin tests, 43 revealed no change in peripheral flow after smoking. The authors concluded that simple skin testing might be a fairly reliable way of screening those people in whom smoking will in all probability not cause any decrease in peripheral blood flow.

KALMANSOHN

**Frye, R. L., and Braunwald, E.: Studies on Starling's Law of the Heart. I. The Circulatory Response to Acute Hypervolemia and Its Modification by Ganglionic Blockade.** J. Clin. Invest. **39:** 1043 (July), 1960.

The cardiovascular response to transfusions was studied in seven normal human subjects before and after ganglionic blockade induced by a constant, continuous intravenous infusion of Arfonad. The cardiac output was not significantly affected by transfusions or by venesection prior to ganglionic blockade, but it did increase after a transfusion during an Arfonad infusion; this latter effect was presumed to be due to a substantial increase in blood volume, associated with a striking increase in the output and work of the left ventricle. The authors conclude that acutely induced hypervolemia stimulates the autonomic nervous system with subsequent reflex venodilatation and depression of myocardial contractility, thereby preventing marked alterations in the circulatory dynamics. When hypervolemia was induced after the activity of the autonomic nervous system had been reduced, more profound hemodynamic changes occurred resembling those changes noted in the Starling heart-lung preparation.

KARPMAN

**Greenberg, J. J., Edmunds, L. H., and Brown, R. B.: Myocardial Metabolism and Postarrest Function in the Cold and Chemically arrested Heart.** Surgery **48:** 31 (July), 1960.

Oxygen utilization, lactic acid metabolism, myocardial oxygen availability, and left ventricular work capacity were studied in a series of 47 dogs in whom 1-hour cardiac arrest was produced utilizing potassium citrate, acetylcholine, or cold. The oxygen consumption of the normothermic, non-working, beating canine heart was 3.7 cc. per 100 Gm. of heart per minute. This decreased sharply from 37 to 30 C. and more gradually from 30 to 5 C. The oxygen consumption of the perfused arrested heart was 1 cc. per 100 Gm. per minute or less during all methods of cardioplegia. Following arrest, however, the

oxygen consumption of the chemically arrested heart did not return to control values. Moreover, during chemical arrest there was a consistent increase in production of lactic acid. Myocardial oxygen availability was significantly lowered during chemical arrest in the unperfused heart. Ventricular work capacity was substantially greater following cold arrest than following chemical arrest. These data suggest that aerobic metabolism continues in the chemically arrested heart, utilizing the interstitial oxygen available and later metabolism continues by anaerobic glycolysis. Since oxygen is not consumed at pre-arrest rates following chemical cardioplegia, this decrease in utilization, which occurs in spite of adequate oxygen availability, implies that the metabolic machinery has been damaged. This is confirmed by the depression of left ventricular function after arrest. This study indicates that cardioplegia of 1 hour is better carried out by cold arrest than by potassium citrate or acetylcholine.

SHEPS

**Hacket, D. G.: Effects of L-norepinephrine on Cardiac Metabolism of Dogs in Hemorrhagic Shock.** Proc. Soc. Exper. Biol. & Med. **103:** 780 (Apr.), 1960.

Eighteen mongrel dogs were premedicated, anesthetized, and had blood samples drawn as well as cardiac catheterization during the control period. Subsequently, sustained hypotension was induced by bleeding the dogs from the femoral artery. After shock was induced, one group of 12 dogs was treated with *l*-norepinephrine and the other six were treated with infusion of whole blood. During the period of shock a negative pyruvate balance was found as well as a decrease in the per cent extraction of lactate. Infusion with *l*-norepinephrine did not change this picture, but reinfusion of whole blood caused immediate reversal of both pyruvate and lactate levels toward normal. An important finding was the variation in glucose during shock and after treatment with blood or norepinephrine so that the main change of significance is the increased arterial level of glucose during shock. The abnormal metabolic pattern of the myocardium responded to the administration of blood by increased blood pressure and, thus, increased cardiac output, as well as decreased vascular resistance of the extremities. L-norepinephrine did not correct the oligemia or the cardiac output and, hence, further increased vascular resistance in the extremities. The use of *l*-norepinephrine alone in the treatment of shock in dogs does not increase per cent of survival because it does not correct the abnormal metabolism of the myocardium and, in fact, actually causes an increase in incidence and severity of myocardial damage according to the authors.

KRAUSE

**Harary, I., and Farley, B.: In Vitro Studies of Single Isolated Beating Heart Cells.** Science **131:** 1674 (June 3), 1960.

Rat heart cells were separated by trypsin treatment and grown attached to glass in a liquid medium. These cells exhibited periodic contractions similar to a whole beating heart. The beating ranged from intermittent, irregular twitches to steady, deep, rhythmic contractions at rates up to 150 per minute. Most of the cells ranged within 30 to 80 beats per minute. When two or more cells were observed in the same microscopic field, they appeared to beat independently. The effect of several drugs and metabolic substrates on these cells was noted. Acetylcholine produced either a marked slowing or complete stoppage of the beating. Recovery ensued in either instance. Eserine had no effect on the beating. When acetylcholine was added the beating slowed to 8 per minute which persisted until ouabain was added, which raised the rate to about 30 per minute. The effects of adenosine triphosphate and other metabolic inhibitors were studied. Observations were sufficiently interesting to suggest that this preparation may provide a unique system for the study of the requirements of the periodic contractibility typical of mammalian hearts.

LEVINSON

**Hicks, R. M., and Kerly, M.: Transaminase Activity in the Perfused Rat Heart.** J. Physiol. **150:** 621 (Mar.), 1960.

Reversible transamination has been demonstrated in the isolated perfused rat heart between aspartic and glutamic acids, but not between other pairs of amino and keto acids. The glutamic/aspartic transaminase activity was only 3-4 per cent of that previously demonstrated in rat heart homogenates and no other transaminase activity was detected. At least a part of the glutamic/aspartic transaminase activity observed during perfusion was due to an enzyme released into the perfusate. Glutamic acid added alone to the perfusate was not utilized, nor was oxaloacetic acid produced during the perfusion. The glutamic acid content of the heart did not increase when it was added to the perfusate but alanine, leucine, and aspartic acid penetrated the heart cells when present in the perfusate. The authors conclude that, at least in the perfused heart, glutamic/aspartic transaminase is not concerned with energy metabolism.

KARPMAN

**Lamb, L. E.: Influence of Aerospace Flight on the Normal Cardiovascular System. Stresses and Effects.** Am. J. Cardiol. 6: 8 (July), 1960.

The normal individual responds to hypoxia at altitudes of 6,000 to 10,000 feet by increasing ventilation. At somewhat higher levels, tachycardia with or without increased stroke volume and then vasodilatation occur in order to maintain tissue oxygen supply. Circulatory collapse develops at 18,000 to 23,000 feet where the critical alveolar $pO_2$ of 30 mm. Hg is reached. Breathing pure oxygen preserves full blood oxygenation to 33,700 feet. At higher levels pressurized oxygen may be required, but its force cannot be permitted to exceed approximately 20 mm. Hg lest venous blood flow to the heart be inhibited and arterial hypotension result. This state may be overcome by wearing a pressurized g-suit. Sudden exposure to an altitude of 50,000 feet or higher allows the rapid loss of blood and alveolar oxygen into the surrounding air. If these circumstances continue for 5 seconds or longer, brain oxygen will be depleted and syncope will ensue, although there will be a lag period of 10 to 15 seconds. The decrease in ambient pressure above altitudes of 27,000 to 30,000 feet allows gaseous nitrogen to escape from the tissues, and the intravascular gas may produce circulatory impairment in any area causing pain or reflex bradycardia. Gravitational (g) force 3.5 times that at sea level is withstood for several minutes, but forces of 5 to 6 g decrease brain and ocular circulation to an intolerable degree in less than 1 minute. G forces are greatest during air maneuvers and depend upon the velocity squared divided by the vehicle's turn radius. Other effects of high g force are sinus tachycardia followed by bradycardia, dependent pooling of blood, edema formation, nausea, hypoglycemia, pain due to visceral dislocation, and collapse. The consequences of prolonged relative immobility on cardiovascular reflexes is an important area for investigation.

ROGERS

**Majia, R. H.: Myocardial Necrosis in Experimental Occlusion of the Portal Vein.** Circulation Research 8: 495 (May), 1960.

Hypovolemic shock was induced in nine mongrel dogs by temporary occlusion of the portal vein. Five other animals that had undergone only a midline incision under pentobarbital anesthesia served as controls. All nine dogs in whom hypovolemic shock was induced recovered initially. In all nine, electrocardiographic signs of subendocardial ischemia appeared within 30 minutes of the beginning of the hypotensive phase. In four dogs these changes reverted to normal once the occlusion of the portal vein was released; in the other five dogs electrocardiographic patterns manifested high lateral myocardial infarction. Levels of glutamic oxalacetic transaminase in serum increased to abnormal values in the five dogs with myocardial necrosis and in one other dog with a liver abscess. Sections of the myocardium showed multifocal necrosis extending from the endocardium to the epicardium.

SCHIRGER

**Malcolm, J. E.: Korotkov's Sounds: Action of the Heart.** Nature 186: 723 (May 28), 1960.

As a result of research upon Korotkov's sounds, the author attempted to explain the action of the human heart. The right and left sides of the heart were each regarded as the mechanical analogue of a reflex klystron. The right and left atria on the one hand and the pulmonary and aortic sinuses on the other constitute cavity resonators wherein contraction and dilation of the walls and apertures generate fields through which the blood flows. The action of the two sides of the heart are similar. The function of the left atrium is to set the blood into motion while that of the orifice of the mitral valve is to produce velocity modulation of the blood entering the left ventricle during diastole. The blood impinges upon the ventricular wall, is reflected upon the aortic valve, with the correct angle of incidence being maintained by the papillary muscles and chordae tendineae. The mitral valve acts as a buncher, the aortic valve and sinuses as a catcher, corresponding to the resonance of the klystron. The function of the autonomic nervous system is that of tuning the resonators, assisted by the apposition of the aortic and mitral valves.

KALMANSOHN

**Martin, J. W., and Schenk, W. G., Jr.: Pericardial Tamponade. Newer Dynamic Concepts.** Am. J. Surg. 99: 782 (May), 1960.

Quantitative studies of the changes in arterial pressure, venous pressure, and left ventricular output were made in dogs as pericardial pressure alterations were recorded following instillation of colored saline into the pericardial sac. This was done under pentothal anesthesia. Increments in pericardial volume were continued until it was thought that circulatory arrest was imminent. The fluid was then removed rapidly, and arterial pressure, cardiac output, and venous pressure were again measured. Peripheral resistance was calculated by dividing mean arterial pressure by cardiac output. It was noted that as cardiac output fell, venous pressure rose. Arterial blood pressure

was still maintained after there had been considerable drop in cardiac output and increase in venous pressure. At first peripheral resistance remained stationary and then later, during the tamponade, increased. Blood pressure fell when it appeared that the animal was at the point of circulatory cessation. It is concluded from this experiment that simple measurement of venous pressure is the best indicator as to the status of the circulation in cardiac tamponade. If blood pressure is depressed it is indicative of imminent circulatory collapse and here rapid pericardial aspiration may be lifesaving.

LEVINSON

**Newman, P. P., and Wolstencroft, J. H.: Cardiovascular and Respiratory Responses to Heating the Carotid Blood.** J. Physiol. **152**: 87 (June), 1960.

Heating the carotid blood in anesthetized cats and in decerebrate cats where the hypothalamus had been removed resulted in a fall of blood pressure and increased respirations. The blood pressure fall was in the range of 40 to 70 mm. Hg and was not associated either with a significant change in heart rate or with detectable perspiration. The effect was not due to a reflex from the carotid sinus or carotid body, since it was present after bilateral section of the lower four cranial nerves. The authors note that recent studies have revealed a similar fall in blood pressure produced by local heating of the medulla and therefore conclude that the heated blood produces its effects by acting on the medulla.

KARPMAN

**Opdyke, D. F., Cannilla, J. E., and Borsuk, G. M.: Effect of Respiration, Asphyxia and Muscle Relaxants on Cardiac Output in the Dog.** Anesthesiology **21**: 244 (June), 1960.

Experiments were conducted on dogs under intravenous pentobarbital anesthesia. Cardiac output was calculated from dye-dilution curves and the effects of respiration, asphyxia, and muscle relaxants were determined. Cardiac output was less at the beginning of lung inflation. During maintained lung inflation the cardiac output increased to the preinflation level. Cardiac output increased about 75 per cent on the average during short periods of asphyxia; muscle relaxants differed in their ability to reduce cardiac output, only d-tubocururaine significantly reducing cardiac output. The authors believe that, if it is desired to maintain output at the highest level, the fraction of the respiratory cycle time devoted to lung inflation must be kept to a minimum. The cardiac output increased to approximately the same level during asphyxia whether or not the dogs were pretreated with muscle relaxants, suggesting that muscle relaxants do not significantly interfere with the mechanisms responsible for the compensatory increase in cardiac output.

KALMANSOHN

## PULMONARY DISEASE

**Cathcart, R. T., Fraimow, W., Nealon, T. F., Jr., and Price, J.: Effect of Intermittent Positive Pressure Breathing on the Cardiac Output of Patients with Chronic Pulmonary Disease.** Dis. Chest. **37**: 222 (Feb.), 1960.

The effect of intermittent positive-pressure breathing on cardiac output was studied, utilizing a group of 31 men, whose ages ranged from 24 to 70 years. All subjects exhibited chronic pulmonary disease, such as pulmonary fibrosis or pulmonary emphysema. All subjects were well acquainted with the use of the intermittent positive-pressure-breathing apparatus. Cardiac output was determined by an indicator-dilution technic using T-1824. Results revealed a small but consistent drop in stroke volume utilizing a peak pressure setting of 20 cm. of water at 20 minutes. Blood pressure and heart rate did not seem to be altered appreciably. Although changes in peripheral resistance were not remarkable, it was noted that a rise in peripheral resistance took place whenever cardiac output fell. Of particular interest was the fact that cardiac output returned to normal, and occasionally to above normal, following the cessation of intermittent positive pressure.

MAXWELL

**Elliott, B. A., Gresham, G. A., and Phear, D. N.: Staphylococcal Invasion of Pulmonary Infarcts.** Brit. M. J. **1**: 1320 (Apr. 30), 1960.

Four cases of patients with pulmonary infarcts complicated by staphylococcal infections are presented. One case terminated fatally. In all four patients, the sputum was positive for staphylococcus pyogenes and the patients were treated with a course of chloramphenicol and erythromycin. One patient was also given tetracycline. These drugs were given following sensitivity tests. The authors feel that patients with pulmonary infarcts are very susceptible to staphylococcal invasion and that when sputum in such patients changes from blood streaked to hemorrhagic pus, staphylococci are almost always present. In addition, the hemorrhagic infarct provides an ideal site for bacterial growth. They stress the importance of septic technic, isolation of infected patients, careful epidemiologic study, and energetic and appropriate antibiotic therapy when staphylococcal invasion does occur.

KRAUSE

# NEWS FROM THE AMERICAN HEART ASSOCIATION

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## AHA Scientific Sessions Program

A total of 165 original scientific papers, selected from a record of 627 abstracts submitted for consideration, will be presented at the 34th annual Scientific Sessions of the American Heart Association. The sessions will be held from Friday, October 20 through Sunday, October 22 in the Americana Hotel, Bal Harbour, Miami Beach, Florida.

These presentations will be made during six sessions on clinical cardiology and at 15 other scientific sessions to be held concurrently throughout the three-day program under sponsorship of the Association's Councils. Additional presentations will be made at panels, symposia, and lectures.

Registrants holding confirmed hotel reservations before September 30 will receive a copy of the program prior to the meeting Abstracts of papers to be presented will be published as Part II of the October, 1961 issue of *Circulation*.

Friday's program includes an opening address by Oglesby Paul, M.D., AHA President; the Conner Memorial Lecture, by Clark H. Millikan, M.D., Professor of Neurology, Mayo Clinic; symposia "Contribution of Phonocardiography to Auscultation," and "Coronary Arteriography"; a lecture on "Biplane Angiography"; concurrent sessions on various cardiovascular subjects; and a program for nurses.

The program on Saturday includes a panel on "Ventricular Arrhythmias"; a lecture on "Closed Chest Cardiac Resuscitation"; the Brown Memorial Lecture, by Robert W. Wilkins, M.D., Professor of Medicine, Boston University School of Medicine; a symposium on "Renal Failure"; and simultaneous sessions on basic science, cardiovascular surgery, and "Compensable Heart Disease, Strain and Trauma."

The Research Achievement Award of the AHA will be conferred on Saturday afternoon. This new award was established following announcement by the Lasker Foundation that no Lasker Award presentations will be made to scientists this year. The winner of the AHA award will receive an honorarium of $1000 and an illuminated scroll.

Conferences on a variety of cardiovascular topics are scheduled for Saturday evening.

Included on Sunday's program are a symposium on "The Role of Hormones in Heart Failure"; panels on "Ventricular Hypertrophy and Bundle Branch Block" and "Newer Electrocardiographic Lead Systems"; a lecture, "ECG Clues Suggesting Myocardial Infarction"; and concurrent sessions on rheumatic fever and congenital heart disease and cardiovascular surgery. Two sessions on cardiovascular films, with introductions and commentary by the author or other authority on the subject, will be held on Sunday.

Registration and accommodation forms may be obtained from the American Heart Association, 44 East 23rd Street, New York 10, New York.

## AHA Annual Assembly Meeting

The 36th Annual Meeting of the AHA Assembly, national delegate and advisory body, will open with a discussion of "The Future Role of the American Heart Association," on Sunday afternoon, October 22, in Bal Harbour, Miami Beach, Florida. The meeting continues through Tuesday, October 24 in the Americana Hotel.

Eight Assembly Panels will meet all day Monday to discuss the Association's programs and policies. The general Assembly convenes again on Tuesday morning to review Panel recommendations and elect the Association's officers and Board members.

The Association's Annual Dinner will be held on Sunday in the Americana Hotel.

Following the AHA Annual Meeting, cardiological sessions under sponsorship of the Puerto Rico Heart Association will be held on October 26-27 in San Juan.

### AHA Grant-In-Aid Applications Deadline is November 1

Applications for Heart Association grants-in-aid for the fiscal year beginning July 1, 1962 must be received by November 1, 1961, at the AHA National Office. The deadline for submitting applications for Research Fellowships and Established Investigatorships was September 15.

All applications for grants-in-aid must be made on forms obtainable from the Associate Medical Director for Research, AHA, 44 East 23rd Street, New York 10, New York. Grants are made to non-profit institutions in direct support of a particular investigator for a specific program of research under his direction. Awards are in support of research in the cardiovascular field or basic sciences for periods up to five years.

### Council on Arteriosclerosis Meeting

Don W. Fawcett, M.D., Professor of Anatomy and Chairman of the Department, Harvard Medical School, will deliver the Lyman G. Duff Memorial Lecture at the Annual Meeting of the Association's Council on Arteriosclerosis on Wednesday, October 18, at 2 P.M. The meeting is scheduled from October 18-20 at the Hotel Balmoral, Bal Harbour, Miami Beach, Florida.

Aaron Kellner, M.D., New York, Chairman of the Council, will address the annual business meeting on Thursday afternoon.

A total of 36 scientific papers will be presented during the Wednesday and Thursday sessions. An additional 18 papers will be presented within the framework of the opening session of the AHA Scientific Sessions.

### North Carolina Scientist Named To Lifetime Research Post

Carl W. Gottschalk, M.D., Associate Professor of Medicine, University of North Carolina School of Medicine, has been named an AHA Career Investigator, the Association's Research Committee announced. He is the 11th medical scientist to receive this award since it was pioneered by the American Heart Association 10 years ago. It provides support throughout their professional lives to scientists of outstanding ability and achievement.

Dr. Gottschalk is conducting studies in kidney function, using micropuncture techniques.

A native of Salem, Va., Dr. Gottschalk received his B.S. degree from Roanoke College in Salem and his M.D. degree from the University of Virginia in 1945. He spent the past year in Copenhagen, working in the laboratory of Dr. H. H. Ussing, a world-famous authority on the metabolism of individual cells of the body, returning to the University of North Carolina this fall.

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The Research Committee also announced the first appointment to be made under a new program which permits a Career Investigator to nominate one Research Fellow to assist in his studies. It named John S. Britten, M.D., to work with Dr. John V. Taggart, AHA Career Investigator, Columbia University College of Physicians and Surgeons, New York, on metabolic aspects of renal function.

### Association's Research Supplemented; Six New Grants-in-Aid Are Awarded

The Colorado Heart Association has provided $7,150 and Orange County (New York) Heart Association $5,500 to supplement the AHA national research program for fiscal 1961-62.

The Colorado funds have been applied to the Grant-in-Aid awarded to Colin H. M. Walker, M.D., University of Colorado Medical School, for studies of the significance of serum mucoproteins and their composition and of the urinary hydroxyproline excretion in rheumatic fever. The Orange County contribution will support a Grant-in-Aid to David

F. Brown, M.D., for studies at Albany Medical College of the role of triglyceride metabolism in ischemic heart disease.

Such contributions from Heart Associations, over amounts regularly assigned by them for research, make possible the support of studies approved by the Association's Research Committee which could not otherwise be covered by the national research budget.

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The Research Committee has also approved the funding of six additional Grants-in-Aid in the amount of $41,550. These became effective last July and bring to approximately $1,877,000 the sums expended in this category for fiscal 1961-62.

### 1959-60 Volumes of "Modern Concepts" Ready

The bound volume of *Modern Concepts of Cardiovascular Disease* covering the years 1959-60 is now available at $3.00 a copy. The volume, indexed according to author and subject, may be obtained from local Heart Associations or through the American Heart Association, 44 East 23rd Street, New York 10, New York.

### Meetings Calendar

September 26-29: American Roentgen Ray Society, Miami Beach. C. A. Good, Mayo Clinic, Rochester, Minnesota.

October 2-6: American College of Surgeons, Chicago. W. E. Adams, 40 East Erie St., Chicago 11, Illinois.

October 3-4: Congress on Occupational Health, Denver. Council on Occupational Health, American Medical Association, 535 N. Dearborn, Chicago 10, Illinois.

October 12-14: International College of Surgeons, Regional Meeting, Atlantic City. W. F. James, 1516 Lake Shore Dr., Chicago 10, Illinois.

October 14-20: International Congress of Neurosurgery, Washington, D.C. Bronson S. Ray, 525 E. 68th Street, New York 21, New York.

October 17-19: International Seminar on Vascular Systems, Miami Beach. John B. Liebler, Heart Association of Greater Miami, 253 S.W. 8th St., Miami 36, Florida.

October 18-20: Council on Arteriosclerosis of the American Heart Association, Bal Harbour, Florida. Jeremiah Stamler, Chicago Board of Health, 54 West Hubbard, Chicago 10, Illinois.

**October 20-24: American Heart Association, Scientific Sessions, October 20-22, Annual Meeting, October 22-24, Bal Harbour, Florida. American Heart Association, 44 East 23rd St., New York 10, New York.**

October 26-27: The Organization of Bio-Medical Instrumentation and Engineering in Universities and Hospitals, Omaha. Office of Medical Extension, University of Nebraska, Omaha 5, Nebraska.

November 13-17: American Public Health Association, Detroit. Berwyn F. Mattison, 1790 Broadway, New York 19, New York.

November 13-18: Canadian Heart Association and National Heart Foundation of Canada, Annual Meeting and Scientific Sessions, Vancouver. J. B. Armstrong, National Heart Foundation of Canada, 501 Yonge St., Toronto, 5, Canada.

November 16-18: International Symposium "Etiology of Myocardial Infarction," Detroit. Thomas N. James, Henry Ford Hospital, Detroit 2, Michigan.

November 25-27: American College of Chest Physicians, Interim Session, Denver. Murray Kornfeld, 112 E. Chestnut, Chicago 11, Illinois.

November 27-29: American Society of Hematology, Los Angeles. John W. Rebuck, Henry Ford Hospital, Detroit 2, Michigan.

November 27-30: American Medical Association, Clinical Meeting, Denver. F. J. L. Blasingame, 535 N. Dearborn, Chicago 10, Illinois.

December 1-2: Symposium on Cinefluorography (3rd), Rochester, New York. Stanley M. Rogoff, University of Rochester Medical Center, Rochester 20, New York.

December 8-9: New York Heart Association, Symposium on the Plasma Membrane, New York. Alfred P. Fishman, 10 Columbus Circle, New York 19, New York.

**1962**

January 29-February 1: American College of Surgeons, Sectional Meeting, Los Angeles. W. E. Adams, 40 E. Erie, Chicago 11, Illinois.

February 7-10: American College of Radiology, New York. W. C. Stronach, 20 No. Wacker Dr., Chicago 6, Illinois.

### Abroad

September 10-15: International Neurological Congress, Rome. G. Alema, Vialo Universita 30, Rome, Italy.

September 11-14: National Congress of Cardiology, San Luis Potosi, Mexico. Jose M. Torre, Av. V. Carranza No. 2405, San Luis Potosi, S.L. P., Mexico.

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**October 7-13: Fourth World Congress of Cardiology, Mexico City. I. Costero, Secretary General, Ave. Cuauhtemoc 300, Mexico 7, D.F.**

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